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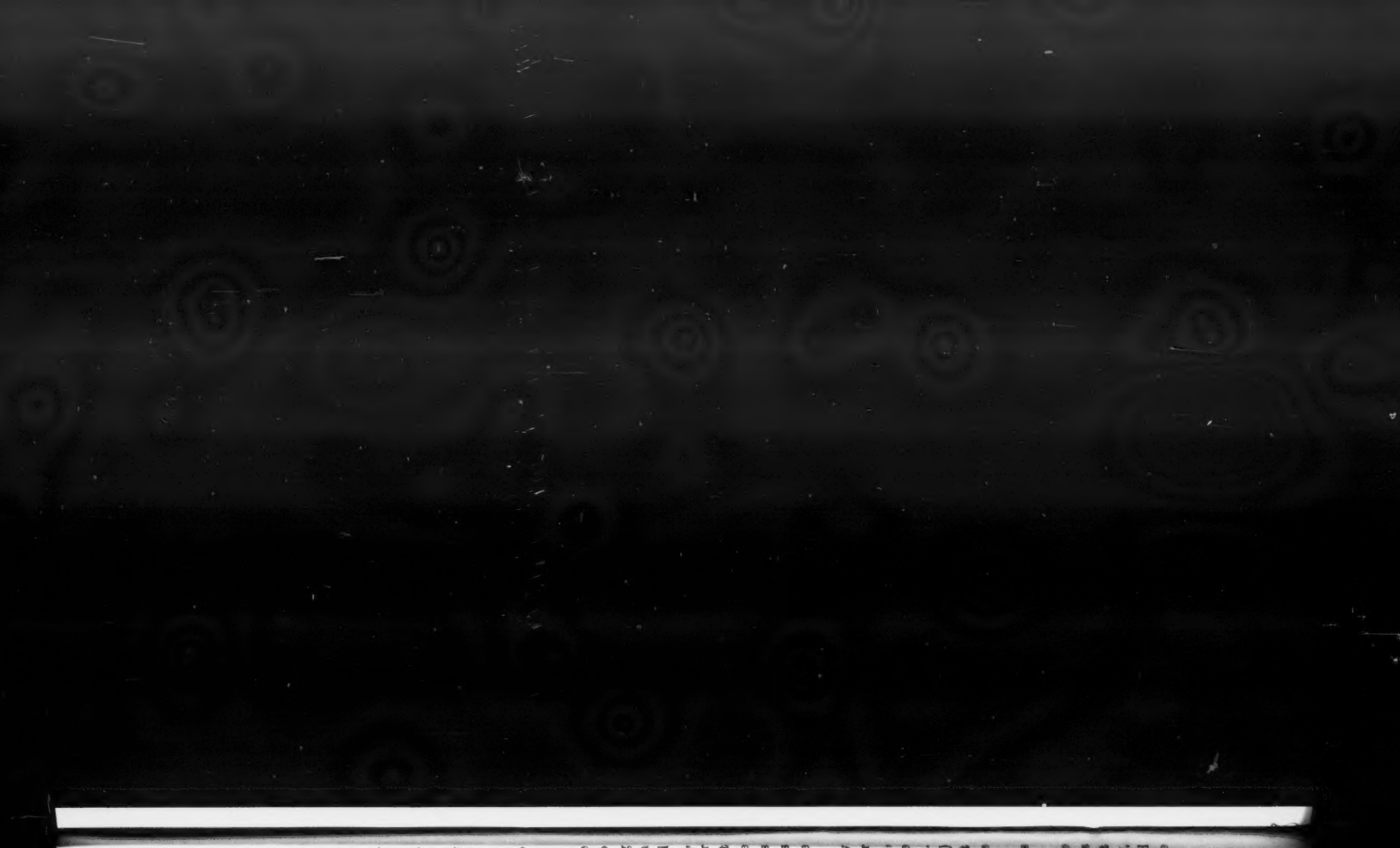

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FROM THE DEPARTMENT OF PEDIATRICS, UNIVERSITY HOSPITAL, UPPSALA. FORMER HEAD: PROFESSOR CURT GYLLENSWÄRD. PRESENT HEAD: PROFESSOR BO VAHLQUIST.

Studies on Carbonic Anhydrase Activity in Children

II. Possibilities of influencing the carbonic anhydrase activity in the blood of premature infants

by

RAGNAR BERFENSTAM

Earlier investigations have shown that in both animals and humans the blood from the fetus and the newborn has a lower carbonic anhydrase activity than the blood from adult individuals. This was shown, among others, by MELDRUM and ROUGHTON, STEVENSON and BERFENSTAM (9, 12, 1, 4).

In a couple of investigations it has been tried to administer the enzyme carbonic anhydrase experimentally to humans. SCHMITT and FRIGGE (11) injected the enzyme preparation Acapnon into a number of patients with heart, kidney and lung diseases. By studying the blood of these persons they found that there was an increase in the alkali reserves accompanied by a simultaneous migration of chloride from the erythrocytes; these changes would recede in less than a day, however. STEVENSON (12), after a transfusion of enzyme-rich blood of adults to premature infants, observed an increase in the activity of the blood of the latter, and also an apparent decrease in the tendency towards cyanosis.

In the present investigation the author has considered more closely the possibility of influencing the carbonic anhydrase activity in premature infants.

Intravenous injections of whole blood from adults into premature infants

The amount of blood injected was about 20 ml per kg of body weight, since this is generally considered to be a suitable quantity for blood transfusions to very young children. On many occasions

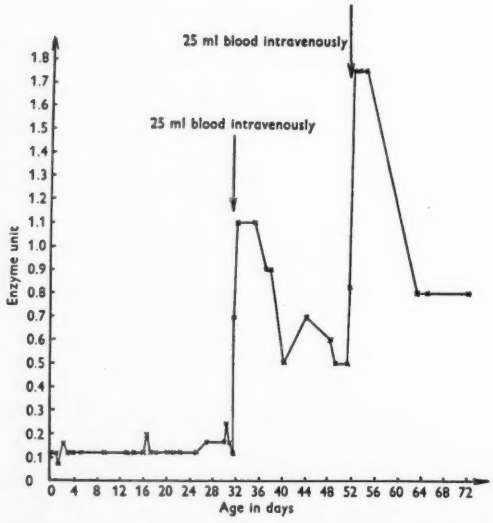

Fig. 1. Enzyme activity of the blood of an infant L—n (weight at birth 1 240 g) who repeatedly received blood intravenously.

it was possible to study the enzyme activity in the blood of the premature infant several days before the transfusion and, as a rule, a blood sample was taken immediately before the transfusion. The enzyme activity was also determined in the blood of the donor. Citrate was added to the blood before transfusion.

Samples of blood were taken from the infant immediately after the transfusion, in 15 minutes and then at intervals of half to two hours for the next twelve hours.

As a result of the blood transfusion (a total of 12) there is in every case a sharp increase in carbonic anhydrase activity. This increase was noticeable immediately after the transfusion, but mostly did not attain the maximum until after 4 hours. The high activity persisted for about 6 hours and then decreased slowly over the next two or three days, but generally remained a little higher than before the transfusion. Fig. 1 shows an example of the effect on the enzyme activity of repeated intravenous blood injections into a premature infant.

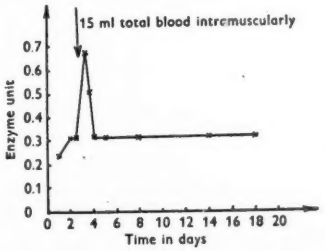

Fig. 2. Enzyme activity after intramuscular injection of blood to an infant W—u (weight at birth 2 130 g).

Intramuscular injections of whole blood into premature infants

It is comparatively difficult to carry out an intravenous blood transfusion on premature infants. On the other hand, intramuscular injections are easy to perform and permit the injections of relatively large volumes of blood. It was therefore interesting to see whether intramuscular transfusions also resulted in an increase of carbonic anhydrase activity.

The blood was injected directly, without the addition of anticoagulants. In general, 10—20 ml were given, equally divided between the two buttocks. As in the case of the intravenous injections it had been possible to study the enzyme activity some days before the transfusion. The samples after transfusion were taken in the way described above, only at longer intervals.

These transfusions (a total of about 20) also gave rise to an increase in activity, though not as high as the intravenous injections. The activity generally reached a maximum after about 4 hours and then for the next few hours decreased to a level often slightly higher than the starting one. Sometimes it was possible to observe a slow increase in activity the week after the intramuscular injection. The diagram in Fig. 2 shows the effect of such an intramuscular injection on the enzyme activity.

Intravenous injection of plasma and serum into premature infants

STEVENSON (12) gave intravenous injections of plasma and serum to premature infants but was not able to observe any change in the enzyme activity after the injections.

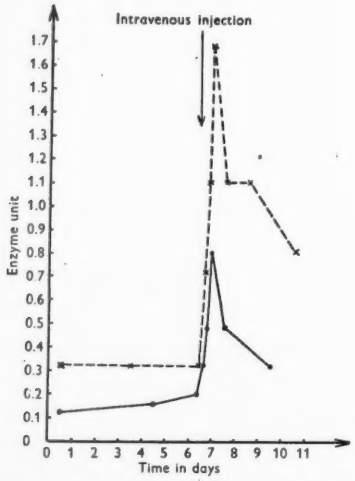

Fig. 3. Enzyme activity after intravenous injections of serum and plasma. The continuous line represents the enzyme activity in an infant S—n (weight at birth 2 160 g) after an intravenous injection of 30 ml of serum. The dotted line represents the enzyme activity in an infant W—n (weight at birth 2 160 g) after an intravenous injection of 35 ml of plasma.

Plasma and serum injections (a total of 3) given by the author had, however, a different result. The volumes injected were the same as for whole blood. Samples were taken from the infants before and at certain intervals after injection. Determinations were also made on the plasma or serum injected, which in every case lacked activity, however.

The results, which were the same whether plasma or serum was injected, showed a clear increase in activity which was already noticeable after some minutes, but which attained a maximum after about 6 hours (Fig. 3). The increased activity lasted a little longer than a day and afterwards decreased to a low value.

Intramuscular injections of plasma and serum into premature infants

Having in mind the results obtained by intravenous serum injections, serum and plasma were also injected intramuscularly. The same amounts as for the intramuscular injections of whole

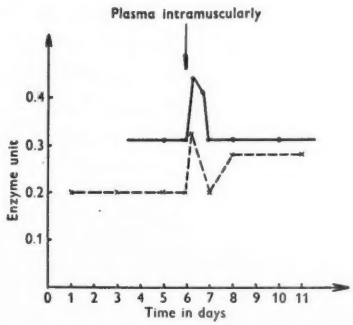

Fig. 4. Enzyme activity after intramuscular injection of plasma. The continuous line represents the activity in an infant V—n (weight at birth 1 230 g) after an intramuscular injection of 12 ml of plasma. The dotted line refers to an infant L—g (weight at birth 2 220 g) who received 15 ml of plasma intramuscularly.

blood were used. The results were an increase noticeable after 4—5 hours. The increase was moderate, but was observed in every case (a total of 11 cases). Its duration was less than a day. The results of two intramuscular plasma injections are shown in Fig. 4.

Discussion

Effect of intravenous or intramuscular injections of whole blood or plasma

As mentioned before, STEVENSON has shown that a transfusion of whole blood from adults into premature infants results in an increased carbonic anhydrase activity in the blood of the latter; he did not, however, study this effect more closely.

The most obvious explanation for the increase in activity is to suppose that the activity from the adult blood is additively transferred to that of the child. There are, however, three circumstances that became apparent in this investigation and that indicate a more complicated state of affairs.

1. The strong increase does not take place immediately after the injection. The highest value for the activity is generally found after hours.

2. A calculation of the expected maximum activity from the known enzyme values of the injected blood and of the blood of the infant before transfusion, the volume of the injected blood and the calculated volume of the total blood of the infant gives a much lower value than the one actually found after transfusion.

The following is an example; the patient was a full term infant:

Name: G. K.

Weight at birth: 3 890 g.

Blood of the child: Calculated volume 330 ml.
Activity before transfusion: 0.96 E.

Injected blood: Volume: 70 ml.
Activity: 3.0 E.

Calculated maximum activity after transfusion:

$$\frac{0.96 \times 330 + 70 \times 3}{400} = 1.32 \text{ E.}$$

Maximum activity found: 2.1 E.

∴ The maximum activity found is greater than the calculated one.

3. The observed increase in activity is of too short a duration to be explained simply as an addition effect. The life of the injected red blood corpuscles was very much longer than the sharp increase in activity of some hours duration, shown in these experiments.

The results obtained from transfusions with whole blood show, that there is reason to believe that some factor other than simple addition of activity — maybe an activating factor in the blood of the donor — must play a rôle in the increase of activity in the blood of the infant.

The question then arises as to which of the components of the blood is the carrier of the activating factor. The effect produced by the intravenous plasma injections indicates that the factor in question must be in the plasma. The initial increase in activity after plasma injections corresponded in magnitude and duration to that produced by whole blood transfusions. After the initial phase of the increase there is, however, sometimes a difference

between plasma and whole blood. In the latter case, as pointed out earlier, the activity curve remains at a somewhat enhanced level, which corresponds roughly to the activity of the surviving erythrocytes of the donor blood. After a plasma transfusion on the other hand, the activity falls again to practically the same value as before transfusion.

No difference could be observed between injections of serum and plasma. As would be expected injections of citrate or physiological saline solutions alone did not produce any increase in activity either, but rather gave rise to an insignificant lowering (dilution effect).

One experiment was carried out in order to test the effect of washed red blood corpuscles, suspended in physiological saline. The injected volume was very small but the number of erythrocytes was the same as that of an amount of whole blood capable of producing an increase in activity. No significant increase in activity could, however, be observed.

The rapid effect of an intramuscular injection of whole blood on the activity was surprising before the results of the plasma injections were known. One might have suspected, that the increase in activity was due to resorption of red blood corpuscles. But for this to take place it would be required that the undamaged erythrocytes could pass from the intramuscular tissues to the blood of the child. It was, in fact, possible to ascertain by means of specially shaped corpuscles (elliptocytes) that such a migration could take place (5). The migration was, however, very slow, since the maximum number of these corpuscles in the blood of the infant could first be observed only after some week. On the other hand it is easy to imagine that the serum from an intramuscular injection could be absorbed immediately into the blood stream. The increase in activity after intramuscular blood injections could therefore be explained from the results of the intravenous plasma injections. In certain of the examined cases after the initial sharp rise a slow increase in activity could be observed during the weeks following the injection (Fig. 2). This increase could possibly be explained on the basis of the red blood corpuscles making their way into the blood of the infant.

When STEVENSON injected serum into premature infants, he did not observe any increase in carbonic anhydrase activity. This discrepancy can be explained by the fact that this author did not carry out serial determinations, but simply determined the activity some days after the transfusion.

Closer study of the activating effect of plasma

The problem of the occurrence of activators and inhibitors in plasma has never been discussed from a clinical point of view. On the other hand plasma from humans and animals has been added in vitro to different enzyme solutions in order to study possible activating or inhibitory effects. LEINER (8) has found that in human plasma there is an inhibitory, thermolabile, as well as an activating, thermostable factor. No activation experiments in vivo have been described.

These activation experiments could be facilitated if it were possible to carry them out in vitro with different plasma fractions. Some experiments described below show, however, that in vitro experiments were not feasible in this case.

Blood from premature infants was mixed in vitro with serum from adults in a proportion corresponding to an intravenous plasma transfusion. Samples for enzyme determinations were taken immediately and then after certain intervals. The mixtures were incubated at 37° C. The enzyme content remained constant all the time, and at the same level as that of the infant's blood before addition of serum. No increase corresponding to the one observed after in vivo transfusion took place.

These experiments have always, therefore, to be performed directly with the infants, and, due to the difficulties involved, only one series of the experiments to be discussed in the following could be carried out. In order to obtain information about the location of the activating factor in the plasma, this was fractionated and the fractions injected separately. The experiment was carried out with an infant incapable of living (myelomeningocele). At first, an intravenous injection of plasma was given. A second portion of plasma was dialysed and given to the same

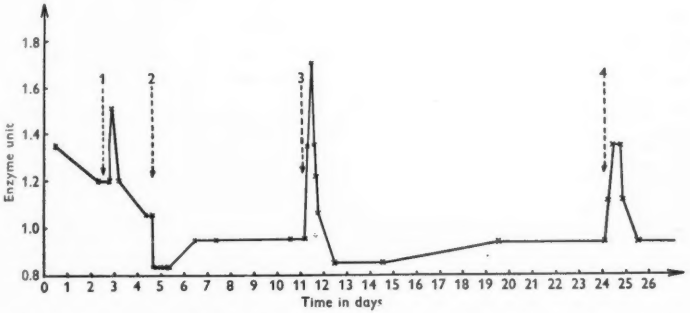

Fig. 5. Enzyme activity in the blood of an infant after intravenous injections of

1. Plasma
2. Dialysed plasma
3. Autoclaved plasma dialysate
4. Desalted and autoclaved plasma dialysate.

infant two days after the first injection. After some further days the previously autoclaved dialysate was injected. The changes in activity can best be seen in Fig. 5. After the plasma injection, the increase obtained was of the same type as observed earlier. The injection of dialysed plasma gave rise to a lowering of the activity (probably a dilution effect). Injection of the autoclaved dialysate, however, produced a sharp increase in activity. In order to eliminate the possibility that the increase was produced by the high electrolyte content of the dialysate, this was desalted according to the method of ÅGREN (13), autoclaved, restored to its physiological salt concentration (by addition of NaCl only) and injected again. The same sharp increase in activity was observed. From this experiment it should then be concluded that the activating factor is *heat stable, dialysable and non-electrolytic in character.*

Further points of view on the possibility of increasing the enzyme activity in premature infants

It has been pointed out earlier that the enzyme carbonic anhydrase is a zinc proteid and it has also been shown that there is a correlation between the enzyme activity and the zinc content

of the blood corpuscles (2). Theoretically it would, then, seem possible that by *increasing the zinc content* the enzyme activity would also increase. Zinc therapy could then be carried out either on the pregnant mother or directly on the newborn infant. In earlier investigations (3) the author has shown, however, that in animals such a zinc therapy resulted in temporarily increased zinc content both of the plasma and of the corpuscles but that the enzyme activity of the blood corpuscles remained unaltered.

It has been possible to obtain an active enzyme preparation from ox blood, which can be administered intravenously. Several authors have carried out *injections of such enzyme preparations* into animals and humans (7, 8, 11). The increased activity of the plasma obtained in this way was shown to be of very short duration. The enzyme clearly disappears very fast and is inactivated possibly through inhibiting substances present in the plasma. (The same condition may prevail in plasma from persons with hemolytic disease in which it has never been possible to demonstrate any enzymic activity). Migration of the enzyme from the plasma to the blood corpuscles thus probably does not take place.

The enzyme action in the plasma is non-physiological, i.e., the presence of enzyme in the plasma probably affects the decomposition of bicarbonate and thus also the acid-base equilibrium.

The only possible ways of obtaining an increase of the enzyme activity in the infants blood therefore seem to be the injection of either *enzyme-rich blood corpuscles from adults* (in which case the effect corresponds to a direct addition of the enzyme from the donor) or of *plasma* or a *factor from plasma* (in which case the effect may be due to an activation).

Some points of view on the effect of an increase in activity in the blood of premature infants

The possible clinical connection between the low enzyme activity in the infants blood and their tendency towards cyanosis has been discussed earlier and it had been concluded that any correlation was doubtful. It would, therefore, also be difficult to determine the effect of an increase in enzyme activity (produced

by transfusion) on the basis of cyanosis. It would be of the greatest value if it would be possible to utilize a reliable objective method to determine the chemical state of blood that is under the influence of the enzyme. It was thought from the observation by NOYON and DE HESELLE (10) that in chicken embryos the yield of CO_2 increased proportionally to the carbonic anhydrase activity. It should then be expected that it would be possible in premature infants to find values for CO_2 output and oxygen saturation which could be correlated with the enzyme activity. Investigations of DAY and DU PAN (6) in premature infants seem to indicate, however, that such a correlation cannot be demonstrated. For the present it is then, only possible to study the effect of the increase in enzymic activity by means of a possible clinical improvement. This, however, presents difficulties in distinguishing between the effect of the transfusion in general and a possible favourable effect due specifically to the increase in enzyme concentration. The investigation described here could perhaps contribute to explain the old observation, that blood and plasma transfusions often seem to be a valuable form of therapy for premature infants in helping these infants to overcome the weakness of the first days of life.

Summary

1. An account of the results of intravenous and intramuscular injections of whole blood, plasma and serum into premature infants is given. In all cases there is an increase of carbonic anhydrase activity in the infant's blood.

2. The cause for the increase in enzyme activity is discussed. This is found to be probably due to an activating factor in plasma; this factor is thermostable, dialysable and seemingly of non-electrolyte character.

3. The possible inconveniences that premature infants could suffer on account of their low carbonic anhydrase activity and the help possibly afforded to these infants by transfusions are discussed.

Études de l'activité de l'anhydrase carbonique chez les enfants.

Possibilités de faire varier l'activité anhydrase carbonique du sang chez les enfants prématurés:

1. On expose les résultats obtenus grace à des injections intra-veineuses et intra-musculaires de sang total, de plasma et de sérum aux enfants prématurés. Dans tous les cas un accroissement de l'activité A. C. du sang des sujets étudiés est obtenu.

2. On discute la cause de cette augmentation. Elle est due probablement à un facteur activant du plasma. Ce facteur est thermostable, dialysable et ne présente pas les caractères d'un éléctrolyte.

3. On discute des inconvénients possibles dont peuvent souffrir les prématurés de leur faible activité anhydrase carbonique et de l'aide que l'on peut offrir à ces enfants grâce aux transfusions.

Studien über Kohlensäureanhydraseaktivität bei Kindern.

Möglichkeiten, die Kohlensäureanhydraseaktivität im Blut frühgeborener Säuglinge zu beeinflussen:

1. Es wird über die Ergebnisse intravenöser und intramuskulärer Injektionen von Vollblut, Plasma und Serum bei frühgeborenen Kindern berichtet. In allen Fällen fand sich eine Zunahme der Kohlensäureanhydraseaktivität in dem Blute der Kinder.

2. Die Ursache der Zunahme der Enzymaktivität wird diskutiert. Verfasser meint, dass sie wahrscheinlich einem Aktivierungsfaktor im Plasma zuzuschreiben ist. Dieser Faktor ist thermostabil, dialysierbar und scheint keinen elektrolytischen Charakter zu haben.

3. Die möglichen Nachteile, die frühgeborene Kinder infolge ihrer niedrigen Kohlensäureanhydraseaktivität haben können, und die Hilfe, die man ihnen eventuell durch Transfusionen gewähren kann, werden diskutiert.

Estudios sobre la actividad de la anhidrasa del ácido carbónico en niños.

Posibilidades de variar la actividad de la anhidrasa del ácido carbónico en niños prematuros:

1. Se exponen los resultados obtenidos gracias a inyecciones intravenosas e intramusculares de sangre total, de plasma y de suero en niños prematuros. En todos los casos se obtuvo un aumento de la actividad de la anhidrasa del ácido carbónico en la sangre de dichos niños.

2. Se discute la causa de este aumento. Es debida probablemente a un factor activante del plasma. Este factor es termoestable, dializable y no presenta los caracteres de un electrolito.

3. Se discuten los inconvenientes posibles de que pueden sufrir los prematuros a causa de su actividad baja en anhidrasa del ácido carbónico y la ayuda que se les pueda prestar eventualmente con transfusiones.

References

1. BERFENSTAM, R.: Studies on Carbonic Anhydrase in Premature Infants. Acta Pædiat. Suppl. 77: 124, 1949.
2. BERFENSTAM, R., The Determination of the Zinc Content of the Blood of Infants and Adults. Upps. Läkareför. förhandl. *54:* 349, 1949.
3. BERFENSTAM, R., Studies on Blood Zinc. Acta Pædiat. Suppl. 87. 1952.
4. BERFENSTAM, R., Studies on Carbonic Anhydrase Activity in Children. I. Enzyme Activity in the Blood of Infants and Children of Different Ages, Particulary in Premature Infants. Acta Pædiat. *41:* 32, 1952.
5. BERFENSTAM, R.: Unpublished data.
6. DAY, R., DU PAN, R. M., Carbonic Anhydrase in the Blood and Kidneys of Premature Infants. Proc. of the Soc. for Ped. Research 1947.
7. VAN GOOR, H.: The Carbonic Anhydrase in Serum. Acta Brev. Neerland. *10:* 218, 1941.
8. LEINER, M., Das Ferment Kohlensäure Anhydratase im Tierkörper III (Hemmende und Fördernde Stoffe im Säugetierblut). Biol. Zentralblatt *64:* 324, 1944.
9. MELDRUM, N. U., ROUGHTON, F. J. W., Carbonic Anhydrase. Its Preparation and Properties. J. Physiol. *80:* 113, 1933.
10. NOYONS, A. K. M., DE HESELLE, P. M. H., Über den Stoffwechsel des Hühnereies und die Bedeutung der Luftkammer. Acta Brev. Neerland. *9:* 170, 1939.
11. SCHMITT, F., FRIGGE, H., Die Wirkung des Acapnons auf das Säure-Basengleichgewicht und den Mineralhaushalt bei verschiedenen Krankheitsbildern. Deutsch. Arch. klin. Med. *185:* 245, 1940.
12. STEVENSON, S. S.: Blood Carbonic Anhydrase in Newborn Infants. J. Clin. Invest. *22:* 403, 1943.
13. ÅGREN, G., DE VERDIER, C. H., On the Paperchromatographic Analysis of Aminoacids and Peptides in Tissue Extracts and Enzyme-Hydrolyzed Proteins. Acta Chem. Scand. *2:* 783, 1948.

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Carbonic Anhydrase Activity in Fetal Organs

by

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This investigation refers to the author's work on the enzyme carbonic anhydrase in the blood of premature infants, published earlier (5). Bearing in mind the very low activity reported then, it was decided to determine the enzyme activity in different organs at different times of embryonic development.

The presence of carbonic anhydrase has been demonstrated in several internal organs from adult humans (8).

ASHBY (1), in 1943, published an investigation concerning the occurrence of carbonic anhydrase in rat embryos: she could not find any activity in the organs. The same author, who has since been especially interested in the enzyme activity of the central nervous system, was able to show in 1948 (2), however, that some activity was present in the medulla oblongata and still higher in the spinal cord in human embryos, but not in the cerebrum. DAY and DU PAN (7) performed some enzyme determinations on embryonic kidneys and found activity there (but no information concerning the degree of development of the embryos was given). DAY and FRANKLIN (6) later showed that the activity in the kidneys of premature infants was similar to that found in kidneys from full term infants. It was furthermore shown by BAKKER (4) that in chicken embryos the carbonic anhydrase activity appeared earlier in the organs than in the blood.

Methods

The enzyme determinations were performed according to the method described earlier by the author (5). The organs were finely divided by trituration with sand in a stone mortar, as described by ASHBY (3). The

mass was then diluted to a concentration suitable for the enzyme determinations. The blood content of the organs was determined by benzidine titration also according to a technique described by ASHBY.

Material

The *fetal material* investigated was taken from organs of 2 to 5 months old fetuses after induced abortion. These organs were preparated immediately, but organs from *premature infants*, which were obtained after autopsy, were analysed 6—12 hours after death.

Results

The results are shown in tables I and II; the enzyme activity of the organs is given as E_{20} per mg wet weight.

Table I.

Enzyme activity in organs of fetuses.

Age (months)	Enzyme activity/mg (wet weight)				
	Kidney	Stomach	Pancreas	Liver	Spleen
2	0.12	0.12			
3	0.12	0.08		0.12	0.16
3	0.20	0.12			
3	0.12	0.00			
4	0.20	0.00		0.48	0.12
4	0.12	0.00			
4	0.12	0.00		0.32	
4	0.28	0.04			
4	0.20	0.08		0.22	
4	0.20				
5	0.20	0.20		0.38	
5	0.32	0.12	0.08		
5	0.36	0.28			
5	0.20	0.28			
5	0.12	0.04			
5	0.32	0.12			
7	0 20	0.44		0.32	

Table II.

Enzyme activity in some organs of premature and full term infants.

	No.	Name	Weight at Birth g	Born before Full Term (weeks)	Age	Cause of Death	Enzyme activity/mg (wet weight)					
							Kidney		Stomach Mucosa	Pancreas	Lung	Blood
							Cortex	Total				
Premature infants	186/48	II K–n	960	12	1 day	Prematurity + Haemorrhag. intracran.		0.34			0.00	0.08
	413/48	G–g	960	11	1 »	Prematurity	0.32	0.32	0.04	0.08		
	132/48	Q–t	1,540	8	1 »	Prematurity + Haemorrhag. intracran.	0.42	0.45			0.10	
	414/48	I L–a	1,080	8	1 »	Prematurity + Atelect. pulm.	0.44	0.48	0.12	0.08		0.12
	415/48	II L–a	980	8	1 »	Prematurity + Atelect. pulm.	0.48	0.32	0.36	0.12		0.16
	332/48	B–l	1,600	6	1 »	Prematurity + Atelect. pulm.		0.58		0.12	0.04	
	470/48	N–n	1,430	2	1 »	Prematurity + Rupt. tent. cerebelli		0.20	0.12			
Full term infants	389/48	W–t	3,650		3 months	Vit. org. cordis	0.84	0.56	1.16	0.30		
	355/48	E–n	4,450		2 »	Abscessus pulm.	0.88	0.76	0.68	0.28		0.80

Discussion

Only in exceptional cases it has been possible to determine the carbonic anhydrase activity in the blood of the fetuses. It was then found to vary between zero and the value found for the smallest of the premature infants, which usually is less than 5 per cent of the adult activity: 2.75 E (5).

Determinations of the blood content of all organs from premature infants examined and of most of the fetal organs were carried out. Since the blood content of the organs from fetuses as well as from premature infants seems to lie generally around 5 per cent and the enzyme activity of the blood is very low, it was, as a rule, superfluous to make corrections for the activity of the blood in the organs.

From the results obtained it is apparent that in general the activity of the enzyme in some organs examined is higher than that of the corresponding blood. It is possible that in the early embryonic stages there is no activity in the blood but only in the organs. In fully developed infants the magnitude of the activity seems to be the same in the organs as in the blood, but in adults the activity of the blood seems to be higher than that of the organs examined.

From the results in table I it seems as though the enzyme activity in fetal *kidneys* is at least as high as in other organs and that it increases with increasing development. This may, as DAY and DU PAN have already pointed out, be related to the ability of the kidneys to produce a strongly acid urine even during fetal life. Due to technical difficulties it has, unfortunately, not been possible to differentiate between the cortex and the medulla of the kidney, but only to obtain values for the whole organ.

It should be noted that the value for the *stomach* in fetuses refers to the whole organ, since it was not possible, as in the case of premature infants, to strip the gastric mucosa for analysis. The value for the enzyme activity, as calculated with the mucosa, should therefore be considerably higher. This fact might be of some interest in connection with the discussion of the importance of the enzyme in hydrochloric acid secretion.

The low activity in the *pancreas* might be related to the fact that during the fetal period the intestinal juice producing activity of this gland is very small, whereas on the other hand the *liver*, which has an important function to fulfill during this period, also shows a higher carbonic anhydrase activity.

One might also observe here that, as it appears from ASHBY's investigations, the organs of the central nervous system which are active during fetal development (namely the medulla oblongata and the spinal cord) also show carbonic anhydrase activity, whereas the cerebrum, whose function is very subordinate during this period, lacks all activity.

The fetal organs were earlier investigated in order to determine the occurrence of digestive enzymes (9). It was shown then, that the presence of pepsin and the pancreatic enzymes could first be demonstrated in the very last months of embryonic life. According to the author's investigations carbonic anhydrase therefore appears earlier in embryonic life than these enzymes. This is not surprising in view of the function of carbonic anhydrase in intermediary metabolism and of the fact that the digestive enzymes hardly have any function before the beginning of extra-uterine life.

Summary

The author has investigated the carbonic anhydrase activity in organs from fetuses and premature infants and shown that the activity in certain organs such as kidney and stomach surpass that in the blood of fetuses of corresponding age. The significance of the enzyme activity in the fetal organs is discussed.

Etudes de l'activité de l'anhydrase carbonique des organes fœtaux.

L'auteur a recherché l'activité de l'anhydrase carbonique dans différents organes provenant de foetus et d'enfants prématurés. Il montre que cette activité dans certains organes — comme par exemple le rein et l'estomac — est supérieure à celle du sang des foetus de même âge. L'auteur discute la signification de l'activité enzématique des organes foetaux.

Kohlensäureanhydraseaktivität in fötalen Organen.

Verfasser hat die Aktivität der Kohlensäureanhydrase in Organen von Embryonen und frühgeborenen Kindern untersucht und zeigt, dass die Aktivität in gewissen Organen, wie Niere und Magen, die im Blut von Föten entsprechenden Alters übersteigt. Die Bedeutung der Enzymaktivität in den fötalen Organen wird diskutiert.

Estudios sobre la actividad de la anhidrasa del ácido carbónico en órganos fetales.

El autor ha investigado la actividad de la anhidrasa del ácido carbónico en diferentes órganos de fetos y de niños prematuros. Demuestra que esta actividad en ciertos órganos es — como por ejemplo en el riñón y el estómago — superior a la de la sangre de fetos de la misma edad. El autor discute el significado de la actividad enzimática de los órganos fetales.

References

1. Ashby, W.: Carbonic Anhydrase in Mammalian Tissue. J. Biol. Chem. *151:* 521, 1943.
2. Ashby, W., Butler, E.: Carbonic Anhydrase in the Central Nervous System of the Developing Fetus. J. Biol. Chem. *175:* 425, 1948.
3. Ashby, W., Chan, D. V.: Determination of Carbonic Anhydrase in Human Autopsy Tissue. J. Biol. Chem. *151:* 515, 1943.
4. Bakker, A.: Über Kohlensäureanhydrase in Normalen und Kataraktösen Linsen. Graefes Arch. f. Ophthalmol. *140:* 543, 1939.
5. Berfenstam, R.: Studies on Carbonic Anhydrase Activity in Children. Acta Pædiat. *41:* 32, 1952.
6. Day, R., Franklin, J.: Renal Carbonic Anhydrase in Premature and Mature Infants. Pediatrics *7:* 182, 1951.
7. Day, R., Du Pan, R. M.: Carbonic Anhydrase in the Blood and Kidneys of Premature Infants. Proc. of the Society for Ped. Research, 1947.
8. van Goor, H.: Die Verbreitung und Bedeutung der Carboanhydrase. Enzymologia *8:* 113, 1940.
9. Werner, B.: Peptic and Tryptic Capacity of the Digestive Glands in Newborns. Acta Pædiat. 35. Suppl. 70 1948.

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Fat Absorption Studies in Children. II

Influence of propylene glycol, lecithin, choline, aureomycin, and low fat diet on fat retention in children

by

LARS SÖDERHJELM

With the idea that a number of factors may influence the amount of fat retained by infants and children, fat balance studies were undertaken to evaluate the possible importance on fat retention of propylene glycol, lecithin, choline, an antibiotic agent (aureomycin), and low fat intake.

Essentially the same procedures and methods were used as reported in a previous study on the effect of heat treatment of milk on fat retention (SÖDERHJELM, 1952). The following features were studied:

A. *Propylene glycol* as used in a commercial vitamin preparation: Four premature infants were studied, three of whom were given cow's milk and the fourth frozen breast milk. Eight fat balance studies were made in 6 to 7 day periods with and without the administration of a vitamin preparation. The results are presented in Table 1.

No change was found in the fat retention in the three infants receiving cow's milk. Slightly greater retention of fat was found in the infant who was given frozen breast milk when the vitamin preparation was withheld. However, the actual retention was within that found in the other infants of this same series.

B. *Lecithin:* Pure vegetable lecithin (Nutritional Biochem. Co.) from one half to two grams daily was given to six patients (three premature infants, one malnourished infant, one with cystic fibro-

Table 1.

Fat absorption in premature infants with (+Vi) and without (−Vi) a vitamin preparation containing propylene glycol.

Case No.	Sex	Birth weight g	Period days	Age days	Weight g	Food	g fat/kg/day		Absorbed fat per cent	Avg. gain g/day
							intake	output		
15	M	1 300	7	31	1 640	Boiled cow's milk +Vi	4.6	1.9	59	24
			7	39	1 810	» » » −Vi	4.5	2.0	56	20
16	M	1 590	7	33	2 090	Boiled cow's milk +Vi	5.6	0.9	85	19
			7	41	2 260	» » » −Vi	5.3	0.7	88	24
17	F	1 370	6	19	1 625	Boiled cow's milk +Vi	4.6	1.8	61	18
			7	27	1 770	» » » −Vi	4.4	1.9	57	13
20	F	1 910	6	10	1 690	Frozen breast milk +Vi	4.8	1.7	65	12
			6½	17	1 810	» » » −Vi	6.3	1.2	81	16

sis of the pancreas, one with celiac disease). Boiled whole cow's milk, evaporated milk, protein rich milk or breast milk were used. The results are given in Table 2.

Fat retention was not altered when lecithin was added to the diet. In one child with cystic fibrosis of the pancreas (Case 26) the retention of fat was decreased when lecithin was added; however, the fat balance periods were only of three days duration.

ADLERSBERG and SOBOTKA (1943) found improved fat absorption with addition of lecithin to the diet in patients with sprue. FÜRTH and SCHOLL (1930) also reported increase in the fat absorption with lecithin in animal experiments. This was confirmed by AUGUR and DEUEL (1947) in studies with rats. TIDWELL (1950) found an increased rate of absorption with added lecithin, which was explained in part by the presence of the phosphatide, which might be needed for an important intermediate step in the resynthesis of triglycerides.

C. *Choline:* Choline chloride was given to only two subjects, one gram daily to an 18 month old child with celiac disease (Case 28, Table 2) and three grams daily to an 8 year old child with steatorrhea of unknown origin (Case 40). A protein rich diet was given to both children. The results are given in Table 2.

No change occurred in the fat retention in these two subjects following choline supplementation. Choline chloride was given to a number of premature infants but vomiting invariably ensued and the use of choline had to be discontinued.

FRAZER (1946) found an increase in fat absorption after administration of olive oil when choline was given and explained this in part to the use of choline for synthesizing phosphatides which are supposedly needed for the resynthesis of triglycerides in fat absorption.

D. *Bacteriostatic agent (aureomycin):* Five children, two premature, otherwise normal, infants, two full term infants and one child with steatorrhea, in periods of 4 to 5 days were given aureomycin and the fat absorption compared with that of control periods. The results are presented in Table 3.

Aureomycin did not influence the retention of fat in these cases. This is not surprising in view of the observations of SPERRY

Table 2.

Influence of lecithin and choline on absorption of fat.

Case No.	Age	Weight g	Period days	Food	Daily supplement	Absorbed fat per cent	Average gain g/day
15.	39 days	1 810	7	Cow's milk	0	56	20
Premature	47 »	1 950	5	» »	0.5 g lecithin	66	40
20.	34 days	2 320	5	Cow's milk	0	90	11
Premature	41 »	2 450	5	» »	0.5 g lecithin	85	54
37.	45 days	1 650	5	Breast milk	0	93	10
Premature	53 »	1 800	5	» »	0.75 g lecithin	81	2
25.	8 mos.	4 050	4	Evap. milk	0	66	35
Malnutrition		4 040	5	» »	1.5 g lecithin	93	37
		4 705	5	» »	0	89	34
26.	3 yrs.	7 510	3	Protein rich milk	0	50	0
Fibrosis of pancreas			3	» » »	2.0 g lecithin	8	
29.	8 mos.	5 620	5	Protein rich milk	0	52	—10
Celiac disease		5 430	5	» » »	2.0 g lecithin	64	38
		5 920	5	» » »	0	55	46
		6 210	5	» » »	2.5 g lecithin	62	50
40.	8 yrs.	19 600	5	Protein rich diet	0	60	
Steatorrhea			5	» » »	3.0 g choline	52	
28.	18 mos.	9 100	5	Protein rich diet	0	78	
Celiac disease			5	» » »	1.0 g choline	75	

Table 3.

Influence of aureomycin on absorption of fat.

Case No.	Age	Body weight g	Period days	Food	Daily supplement	Fat		Absorption per cent
						intake	output	
35. F.	3 weeks	1 570	5	Breast milk	None	59.4	8.8	85
Premature	4 weeks	1 760	5	» »	Aureomycin 0.05 g	63.5	7.5	89
38. M.	3 weeks	1 700	5	Breast milk	None	37.5	2.5	93
Premature	1 mo.	1 860	4	» »	Aureomycin 0.05 g	28.4	1.6	94
43. M.	7 mos.	6 950	6	Cow's milk formula	None	88.9	9.8	89
Myelomeningocele			5	» » »	Aureomycin 0.1 g	70.2	6.1	91
44. F.	7 mos.	7 520	6	Cow's milk formula	None	82.1	9.0	89
Seq. meningitidis			5	» » »	Aureomycin 0.1 g	70.2	7.4	89
40. M.	8 yrs.	19 600	5	Potein rich diet	None	116	65	57
Steatorrhea			4	» » »	Aureomycin 0.25 g	106	11.2	89
			5	» » »	None	228	92	60
			5	» » »	Aureomycin 0.25 g	98	77	62

Table 4.

Fat absorption in children on a low fat diet.

Case No.	Body weight g	Period days	Fat		»Absorption» per cent	Weight gain g/day
			intake g/day	output g/day		
19. F.	3 050	3	0.69	0.50	27	33
Birth weight 2 170 g	3 180	3	0.64	0.39	39	25
25. F.						
Birth weight 2 130 g	2 100	5	0.38	0.09	77	50
30. M.	2 290	5	0.21	0.11	47	10
Birth weight 1 350 g	2 570	5	0.28	0.14	51	4
27. F.	4 960	5	0.95	0.24	75	10
Birth weight 3 320 g						
39. M.	4 170	4	0.33	0.22	34	45
Birth weight 4 120 g	4 350	5	0.26	0.17	36	28
	4 540	5	0.31	0.22	31	26
42. M.	3 240	5	1.72	0.49	72	52
Birth weight 2 560 g	3 570	6	0.74	0.28	62	53
28. M.	6 500	4	0.67	1.04	Negative balance	—10
Celiac disease						
29. F.	7 250	10	0.43	0.50	Negative balance	7
Celiac disease						

(1924, 1929—30, 1932), who found that only a small fraction of the fat of feces of dogs could be derived from bacteria within the intestines.

E. *Low fat diet:* A mixture of skimmed milk and dextrimaltose or sucrose with a total intake of fat of less than 2 grams daily was given to eight children, two of whom had celiac disease. The results of fat balance studies are presented in Table 4.

In six infants the amount of fat in the stools was less than that consumed while on a very low fat intake. On the other hand, in two patients with celiac disease (Cases 28, 29, Table 4) the output of fat was greater than the intake when on the low fat regimen. The true significance of this is not known, though a disturbance in the intermediary metabolism of fat might be the explanation (WEIJERS and VAN DE KAMER 1950).

Discussion and Summary

In a previous study with premature infants designed to ascertain the effect of the treatment of milk on the efficiency of fat retention, it was found that the type of heat treatment of cow's milk or breast milk did not influence fat absorption. On the other hand, when these premature infants were maintained on breast milk the amount of fat retained was greater than when on cow's milk. In part one may explain the superior retention of fat in premature infants fed breast milk to differences in unsaturated fatty acid and mineral contents of cow's milk and breast milk (HOLT 1935). Nevertheless there may be factors other than the types of milk which influence fat absorption.

No differences in fat retention were observed following the administration of propylene glycol as used in a polyvitamine preparation, lecithin, choline, or aureomycin. Even with low fat diets there is a positive retention, indicating little if any endogenous fat excretion in the stools. Only in disorders associated with steatorrhea was the fat balance negative when the patients were on a low fat diet.

Études sur l'absorption des graisses chez les enfants. II. Influence de: Propylène glycol, lécithine, choline, auréomycine, et du régime de restriction des graisses sur la rétention des lipides chez les enfants.

L'auteur n'a pas observé de différences concernant la rétention des graisses après administration de propylène glycol contenu dans une préparation polyvitaminée, de lécithine, de choline, ou même d'auréomycine. Même lorsque l'on donne un régime pauvre en graisses, on observe une rétention de celles-ci, indiquée par une excrétion endogène très faible dans les selles. Ce n'est que dans les affections s'accompagnant de stéatorrhée que la balance des graisses a été négative, et cela même si les malades observés étaient soumis a un régime pauvre en corps gras.

Studien über Fettabsorption bei Kindern: II. Der Einfluss von Propylenglykol, Lezithin, Cholin, Aureomyzin und fettarmer Diät auf die Fettretention bei Kindern.

Der Verfasser beobachtete keine Unterschiede der Fettretention nach Zuführung von Propylenglykol, wie es in einem Polyvitaminpräparat verwendet wird, Lezithin, Cholin oder Aureomyzin. Auch bei fettarmer Diäten besteht eine positive Retention, die eine geringe, wenn überhaupt eine, endogene Fettexkretion in den Stühlen anzeigt. Nur bei Erkrankungen in Verbindung mit Steatorrhoe war die Fettbilanz negativ, wenn die Patienten auf eine fettarme Diät gesetzt waren.

Estudios sobre la absorción de grasa en los niños. II. Influencia del glicolpropileno, lecitina, colina, aureomicina y dieta pobre en grasa sobre la retención de grasa en los niños.

No se han apreciado diferencias en la retención de grasa con la administración de glicol-propileno como se emplea en los preparados polivitamínicos, lecitina, colina o aureomicina. Incluso con una dieta pobre en grasa se halla una retención positiva y tan solo en los trastornos asociados con esteatorrea hay un balance en grasa negativo cuando los pacientes están sometidos a una dieta pobre en grasa.

References

Adlersberg, D. & Sobotka H.: Influence of lecithin feeding on fat and vitamin A absorption in man. J. Nutr. *25:* 255, 1943.

Augur, Virginia, Rollman, Hilda & Deul Jr., H.: The effect of crude lecithin on the coefficient of digestibility and the rate of absorption of fat. J. Nutr. *33:* 177, 1947.

Frazer, A. C.: Effect of choline on the intestinal absorption of fat. Nature *157:* 414, 1946.

——: Fat metabolism and the sprue syndrome. Brit. M. J. *2:* 769, 1949.

FÜRTH, O. & SCHOLL, R.: Über den Einfluss von gallensauren Salzen auf Diffusions- und Resorptionsvorgänge. Ein Beitrag zur Physiologie der Vettverdauung. Biochem. Zschr. *222:* 430, 1930.

HOLT Jr., L. E., TIDWELL, H. C., KIRK, C. M., CROSS, DOROTHEA & NEALE, SARAH: Studies in fat metabolism. Fat absorption in normal infants. J. Pediat. *6:* 427, 1935.

SPERRY, W. M. & BLOOR, W. R.: Fat excretion. II. The quantitative relations of the fecal lipoids. J. Biol. Chem. *60:* 261, 1924.

SPERRY, W. M.: The partition of fecal lipids in bile fistula dogs. J. Biol. Chem. *85:* 455, 1929—30.

SPERRY. W. M. & ANGEVINE, R.: The secretion of lipids into the intestine. J. Biol. Chem. *96:* 769, 1932.

SÖDERHJELM, L.: Fat absorption studies in children. I. Influence of heat treatment of milk on fat retention by premature infants. Acta pædiat. *41:* 20, 1952.

TIDWELL, H.: Mechanism of fat absorption as evidenced by chylomicrographic studies. J. Biol. Chem. *182:* 405, 1950.

WEIJERS, H. A. & VAN DE KAMER, J. H.: De vetresorptie van gezonde en zieke zuigelingen en kinderen in het bijzonder van coeliakiepatienten. Diss. Utrecht, 1950.

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Fat Absorption Studies in Children. III

Fat tolerance tests

by

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The determination of the intestinal absorption of fat is an important examination in many diseases in children. Fat balance studies over a period of five days or more give exact information, but require considerable time and effort. In contrast a fat tolerance test is simpler to perform and requires less time. In the latter test a certain amount of fat is given orally and the serum content of fat is determined for some hours afterwards. However, the increase in the serum depends, not only upon the rapidity of the absorption but also upon the rate at which fat is utilized or deposited in the tissues, i. e., a fat tolerance test gives only a rather uncertain estimation of the absorption.

The following methods have been used most commonly:

1. Vitamin A tolerance tests:

Since vitamin A is fat soluble it is possible to estimate the absorption of fat with a tolerance test using a high dose of vitamin A in oil.

MAY and LOWE compared (1948) the results of tolerance tests when the vitamin A was dissolved in oil and when emulsified. In normal children the difference was slight, but in patients with celiac disease or fibrosis of the pancreas the serum content of vitamin A was considerably lower when the oily preparation was administered.

PRATT and FAHEY (1944) consider that one single determination of the serum content of vitamin A four to five hours after ingestion of an oily preparation of vitamin A, is sufficient to evaluate the absorption. If the figure is compatible with a normal increase, fibrosis of the pancreas is excluded with a probability of 95 per cent,

CLIFFORD (1948) and SOBEL and coworkers (1949) have studied the absorption of concentrated oily solutions of vitamin A in premature and

newborn infants. They gave as small a volume as 0.5 ml of oil on an empty stomach. From the small increase in the serum fat content the authors concluded that the absorption of fat in these infants is poor.

In addition, WEIJERS and VAN DE KAMER (1950) have studied the fat absorption in parallel experiments with vitamin A tolerance tests and fat balance studies. They found that in most instances it was possible to state whether there was a disturbance of absorption, but impossible to judge the character or the severity of this disturbance.

The methods commonly used for the determination of vitamin A is that given by MAY, MCCREARY and BLACKFAN (1940) and requires at least 1 ml of serum, or BESSEY's micromethod for 0.03—0.06 ml serum (1946). These methods are rather complicated for occasional use in small laboratories.

2. A count of chylomicrons has been used by several investigators (FRAZER and STEWART 1939, FRAZER 1947, BOHM, GERNANDT and HOLMGREN 1941, TIDWELL 1950, ELGHAMMER 1950 a. o.). Although only a drop of blood from the finger tip is required the practical difficulties of the technique are great. SCHULTZ (1912) observed the turbidity of serum directly, using a method given by SCHELBLE (1908), and estimated the fat absorption from the degree of visible lipemia. MORETON's nephelometric procedure (1950) is more exact and rather simple, but requires considerable volumes of serum and is thus not suitable in children. The concentration of phospholipids in the serum moreover determines whether the fat is visible or not (AHRENS and KUNKEL 1949).

3. Determination of the total serum fat with KUNKEL's turbidimetric procedure (1948) is simple and requires 0.05—0.2 ml serum. This method has been used with success in fat tolerance tests in adults by THORLING (1950). Principally, serum is added to a solution of phenol and the turbidity is measured in a photocolorimeter.

In the following paper experiments with KUNKEL's turbidimetric method are reported.

Materials and methods

Fat tolerance tests were performed in healthy infants, infants with malformations outside the gastrointestinal tract, a few children with poor fat absorption and a few older children. Corn oil (Mazola) was used, as it is rich in unsaturated fatty acids and easily absorbable. The children received 1.2—3.0 ml per kg body weight, the smaller volumes being given to the older children. The oil was given alone or together with a skimmed milk formula with a very low fat content.

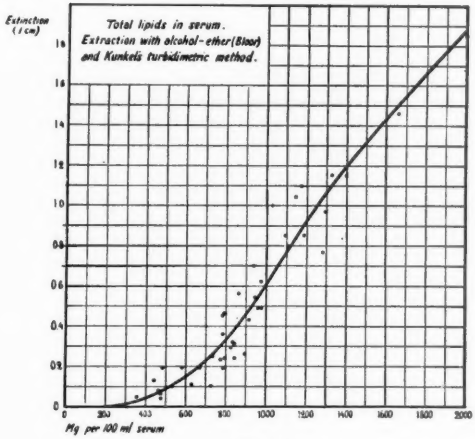

Fig. 1.

Capillary blood was taken from the heel or finger tips before the oil was given and at varying intervals afterwards. The total fat of the serum was determined in photocolorimeter (SPEKKER) after addition of phenol using a red or neutral filter. Since hemolyzed blood samples give too high values they are unsuitable. Arbitrary units were used without any reference to a $BaSO_4$ standard. A comparison of these units and determinations of total fat in the same serum by BLOOR's method was made by THORLING, who did not find a straight linear relationship as is seen in Figure 1.

Results

Fat tolerance tests in children with a probable normal fat absorption are shown in Table 1. The figures are given as mg fat per 100 ml serum, calculated from the curve (Fig. 1), and are thus only approximate.

In Table 2 a comparison is made between results of fat tolerance tests and fat absorption according to balance experiments (5—7 day period). As is seen in the table there is a relatively good agreement between these methods in most cases. That the amount of ingested fat is important, will be seen from Case 3.

Table 1.

Fat tolerance tests in children with normal fat absorption.

No.	Age	ml oil/kg body weight	Fat in serum mg per 100 ml			
			0 hr	2 hrs	3 hrs	5 hrs
1	6 weeks	2.3	625	900	750	625
2	2 months	2.3	610	700	710	670
3	4½ »	2.5	730	850	1 060	950
4	9 years	1.2	640		700	690
5	11 »	1.3	550		650	690

This patient showed a good increase when he received 2.5 ml oil per kg body weight, though the fat absorption according to the balance experiment was poor. When the same patient got 1.3 ml oil per kg the increase in the fat content of the serum was small, although the balance was somewhat better at that time. Case No. 4 had an improved fat tolerance test parallel with a better fat balance after prolonged dietary treatment. Patient No. 8 showed a good fat balance but a rapid and transient increase in the tolerance test. SCHULTZ (1912) also found this in malnourished infants put on adequate diets.

In the experiments described the oil was given alone on an empty stomach. In Table 3, fat tolerance tests are shown where the infants got oil alone or oil together with a skimmed milk formula. The increase in the total fat was evident in most instances. Only patients Nos. 2 and 3, 3 weeks resp. 2 months old, did not show any increase after oil alone. Oil together with skimmed milk, however, caused an increase also in these patients. In all cases studied, oil alone caused less increase than oil with skimmed milk. However, the difference was rather small, especially in the older infants.

In order to determine if the smaller increase after oil alone depends upon a poor or delayed fat absorption, three infants were given oil alone and skimmed milk formula alone for one week, and the same amount of oil together with the formula for another week. The fat balance was studied during these periods and the

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Table 2.

Fat tolerance test and fat balance study in the same patient.

No.	Diagnosis	Age	Ml oil per kg body weight	Fat in serum mg per 100 ml					Balance experiment Fat absorption per cent
				0 hr	1 hr	2 hrs	3 hrs	5 hrs	
1	Fibrosis of pancreas	2 years	2.3	440			470		10
2	» » »	1 year	2.2	505	520		540	520	39
3	Steatorrhea	8 years	1.3	505			470	470	60
	Same patient	8 »	2.5	520		550	625	680	49
4	Celiac disease	1 year	2.5	550		600	610		66
	Same patient	13 months	2.6	640		665	770	790	89
5	Celiac disease (recovering)	2 years	2.0	505			665	625	78
6	Subnutrition	1 year	3.0	540		610	680		90
7	Prematurity	2 months	2.5	425			665	640	93
8	Subnutrition	6 »	2.5	580		680	565	550	94

Table 3.

Fat tolerance tests in infants receiving oil alone and oil with a skim milk formula.

No.	Age	Diagnosis	Diet	Ml oil/kg body weight	Fat in serum mg per 100 ml		
					0	3 hrs	5 hrs
1	7 days	Mongoloid	oil	2.6	520	580	490
	9 »		oil + skim milk	2.6	470	540	505
2	3 weeks	Healthy	oil	2.3	650	665	565
	»		oil + skim milk	2.3	680	730	700
3	2 months	Prematurity	oil	2.5	550	520	505
			oil + skim milk	2.5	425	665	640
4	2 »	WERDNIG-HOFFMANN's disease	oil	2.5	565	665	650
			oil + skim milk	2.5	720	880	830
5	6½ »	Ulcerous colitis	oil	1.9	625	755	700
			oil + skim milk	1.9	520	780	<850[1]
6	9 »	ULRICH-BONNEVIE's syndrome	oil	1.2	730	800	720
			oil + skim milk	1.2	<700[1]	770	760
7	9½ »	Eczema	oil	1.3	540	745	610
			oil + skim milk	1.3	505	625	665

[1] Slight hemolysis.

Table 4.

Fat balance experiments (balance period 5 days) with oil together with skim milk or given separately.

Name	Fat absorption per cent	
	oil with skim milk	oil alone
B. J.	94	68
A. M.	90	85
B. S.	88	87

results shown in Table 4. Only one infant exhibited a considerable difference in fat absorption.

Discussion

Before fat is absorbed from the gastrointestinal tract it has to be emulsified. This emulsification normally occurs in the intestines through the influence of bile, intestinal and pancreatic juices. Fat ingested alone on an empty stomach depresses the production of gastric and pancreatic juices (ÖBRINK 1948 and others). According to the experiments related in this paper infants absorb small amounts of oil better if the oil is given with other food than when oil is given alone. Thus, if fat is given alone the emulsification and also the absorption seems to be impaired. In fat tolerance tests it is necessary to combine the fat with some other food, e. g., skimmed milk formula to infants, tea and toast to older children and adults. It is clear that infants ought to get vitamin preparations in oily solution together with their meals, as was pointed out earlier by KÜSTER (1939).

Fat tolerance tests with determination of the total fat in serum may give useful information on the fat absorption in children. The fat content is influenced, however, not only by the rapidity of the absorption but also by the pyloric mechanism, tonus of the intestines, deposition of fat in the tissues, etc. A fat tolerance test therefore cannot be anything more than a rough screening method and should be supplemented with balance studies in appropriate cases.

Summary

A short review is given on the methods used in fat tolerance tests in children.

The determination of the total fat in serum according to the turbidimetric method of KUNKEL and AHRENS is very simple and may be used as a screening test when poor fat absorption is suspected.

Études sur l'absorption des graisses chez les enfants. III. Test de tolérance aux graisses.

L'auteur expose, au cours d'une brève revue générale, les méthodes employées dans la mesure des tests de tolérance aux graisses chez les

enfants. La mesure des lipides totaux du sérum selon la méthode de Kunkel & Ahrens est trés simple et peut etre employée comme test global lorsque l'on suspecte une diminution du pouvoir d'absorption des graisses.

Studien über Fettabsorption bei Kindern. III. Prüfung der Fetttoleranz.

Der Verfasser gibt einen kurzen Überblick über die Methoden, die bei Prüfungen der Fettoleranz von Kindern angewandt werden. Die Bestimmung des Gesamtfetts im Serum nach der turbidimetrischen Methode von Kunkel & Ahrens ist sehr einfach und kann als ein entscheidender Test benutzt werden, wenn Verdacht auf Störung der Fettabsorption besteht.

Estudios sobre la absorción de grasa en niños: III. Pruebas de sobrecarga de grasa.

Se da un corto resumen de los métodos que se emplean en las pruebas de sobrecarga de grasa en niños. El análisis de la cantidad total de grasa con el método turbidimétrico de Kunkel-Ahrens es como se vé, sencillo y presta buenos servicios como simple orientación cuando se sospecha una absorción de grasa baja.

References

AHRENS, EDWARD H., Jr. and HENRY G. KUNKEL: The stabilization of serum lipid emulsions by serum phospholipids. J. Exp. M. *90:* 409, 1949.

BESSEY, OTTO A., OLIVER H. LOWRY, MARY JANE BROCK and JEANNE A. LOPEZ: The determination of vitamin A and carotene in small quantities of blood serum. J. Biol. Chem. *166:* 177, 1946.

BOHM, E., B. GERNANDT and Hj. HOLMGREN: Investigations of the daily rhythms in the production of chylomicrones in man on the supply of fat. Acta med. scand. *106:* 579, 1941.

CLIFFORD, STEWART and KATHLEEN F. WELLER: The absorption of vitamin A in prematurely born infants. Pediatrics *1:* 505, 1948.

ELGHAMMER, W. ROBERT, JOHN M. REICHERT and HERBERT F. PHILISBORN, Jr.: Postprandial lipemic response in infants and children. Pediatrics *5:* 621, 1950.

FRAZER, A. C. and H. C. STEWART: Chylomicrograph technique. J. Physiol. *95:* 21, 1939.

FRAZER, A. C.: Lipolysis and fat absorption. J. Physiol. *102:* 329, 1947.

KUNKEL, HENRY G., EDWARD H. AHRENS, Jr. and WILLIAM J. EISENMENGER: Application of turbidimetric methods for estimation of gamma globulin and total lipid to the study of patients with liver disease. Gastroenterology *11:* 499, 1948.

KÜSTER, F.: Die Resorption kleiner Fettmengen durch den Säuglingdarm. Zschr. Kinderh. *60:* 458, 1939.

MAY, CHARLES D., K. D. BLACKFAN, J. F. MCCREARY and F. ALLEN, Jr.: Clinical studies of vitamin A in infants and in children. Am. J. Dis. Child. *59:* 1167, 1940.

MAY, CHARLES D. and CHARLES U. LOWE: The absorption of orally administered emulsified lipid in normal children and in children with steatorrhea. J. Clin. Invest. *27:* 226, 1948.

MORETON, JOHN: Chylomicronemia, fat tolerance, and atherosclerosis. J. Lab. & Clin. M. *35:* 373, 1950.

PRATT, EDWARD L. and KATHLEEN R. FAHEY: Clinical adequacy of a single measurement of vitamin A absorption. Am. J. Dis. Child. *68:* 83, 1944.

SCHELBLE: Untersuchungen über die Fettresorption des Säuglings. Münch. med. Wschr. *10:* 492, 1908.

SCHULTZ, PAUL: Ein Beitrag zur Frage der Verdauungslipämie. Zschr. Kinderh. *4:* 63, 1912.

SOBEL, A., LOTTIE BESMAN and B. KRAMER: Vitamin A absorption in the newborn. Am. J. Dis. Child. *77:* 576, 1949.

THORLING, LEIF: Personal communication (1950).

TIDWELL, H.: Mechanism of fat absorption as evidenced by chylomicrographic studies. J. Biol. Chem. *182:* 405, 1950.

WEIJERS, H. A. and J. H. VAN DE KAMER: De vetresorptie van gezonde en zieke zuigelingen en kinderen in het bijzonder van coeliakiepatienten. Diss. Utrecht, 1950.

ÖBRINK, K. J.: Studies on the kinetics of the parietal secretion of the stomach. Acta physiol. scand. *15:* Suppl. 51, 1948.

Received 11.6. 1951.

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Akademiska Sjukhuset
Uppsala. Sweden.

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Neue Befunde zur Diagnose und Klinik der chronischen Aminoacidurie mit Cystinspeicherung[1]

von

HELMUT WEYERS

Die Diagnose der Aminoacidurie mit Cystinspeicherung ist in vivo bisher nur in wenigen Fällen gestellt worden, obgleich das Leiden häufiger zu sein scheint, als die spärlichen Mitteilungen der letzten Jahre vermuten lassen. Sofern man nicht durch systematische Urinanalysen mit Hilfe der Papierchromatographie (MARTIN, DENT) aus einem grossen Krankengut Einzelfälle ermitteln kann (DENT, BICKEL), wird nur eine gute Kenntnis der klinischen Symptomatologie die rechtzeitige Diagnose ermöglichen. Im folgenden soll daher unter besonderer Berücksichtigung der Hinweise, die die Verdachtsdiagnose sichern helfen, eine einfache bioptische Methode als diagnostisches Hilfsmittel beschrieben werden.

In den mitgeteilten Frühfällen ist man übereinstimmend im 2. Lebenshalbjahr durch eine Vitamin-D-resistente Rachitis mit epiphysären Strukturveränderungen vom Honigscheibentypus auf die renale Rachitis hingewiesen worden, welche durch eine die physiologischen Grenzen übersteigende Hyperphosphatämie und Abfall der Blutcalciumwerte gekennzeichnet ist. Ein konstanter Urinbefund mit geringer Eiweisstrübung, Erythrocyt- und Zylindrurie sind wie eine — oft nur passagere — Glycosurie für die chronische Aminoacidurie besonders suspekte Symptome. Mit zunehmendem Alter wird auch das Längenwachstum mitbetroffen und mit Verunstaltungen der langen Röhrenknochen das Vollbild der

[1] Nach einem Vortrag auf der 4. Tagung der Nordwestdeutschen Gesellschaft für Kinderheilkunde am 27. Mai 1951 in Kiel.

chronischen Aminoacidurie mit Cystinspeicherung ausgeprägter. Merkwürdigerweise sind von der Cystinspeicherkrankheit in der Regel blondhaarige Kinder (Abb. 1) blutsverwandter Eltern befallen, wie auch aus den genealogischen Aufzeichnungen unserer Beobachtung (Abb. 2) hervorgeht. Über die Erbbiologie dieser eigenartigen Stoffwechselstörung liegen nur wenige Untersuchun-

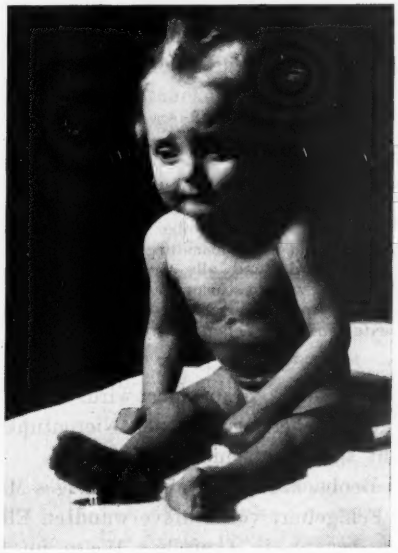

Abb. 1. Einjähriges, blondhaariges Mädchen mit chronischer Aminoacidurie vom Cystinosetyp. Statischer Entwicklungsrückstand, Hypotonie der Muskulatur, schlaffe, faltige Bauchdecken.

gen vor. Neben recessiver Erbfolge ist ein unregelmässig dominantes Auftreten beobachtet worden. Auf Einzelheiten der Erbfolge kommen wir in Verbindung mit Stoffwechseluntersuchungen a. O. ausführlicher zurück.

Das Wesen der Erkrankung kann nach den heutigen Kenntnissen als eine Aminosäuren(AS)-Stoffwechselstörung aufgefasst werden, wobei offenbar durch Fehlsynthese oder Verwertungsstörung bestimmte AS vermehrt im Urin ausgeschieden werden und das (schwerlösliche) Cystin im Gewebe der grossen Drüsen,

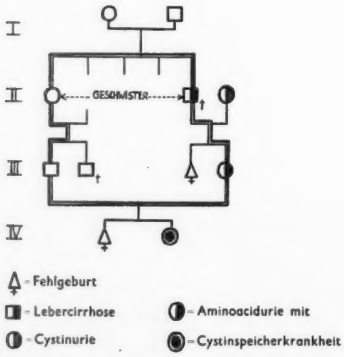

Abb. 2. Stammbaum bei Aminoacidure mit Cystinspeicherung. Der doppelt konturierte Kreis zeigt die Blutsverwandtschaft der Eltern. Offenbar liegt aber ein dominanter Erbgang vor, wobei die Anlage von der Grossmutter (= Cystinurie) auf Mutter (= Aminoacidurie) und Kind (= Cystinspeicherkrankheit) übertragen wurde und alle Grade der Cystindiathese, von der harmlosen Cystinurie bis zur Cystinspeicherkrankheit, der Schwere folgend, aufgetreten sind. Erwähnenswert erscheint, dass der Grossvater (mütterlicherseits) an einer Lebercirrhose gestorben ist.

der Knochen und des RES gespeichert wird. Die Frage, inwieweit hierbei die Organspeicherung von der Nierenfunktion abhängt, kann noch nicht sicher entschieden werden.

Eine eigene Beobachtung, die ein einjähriges Mädchen betraf, das nach einer Fehlgeburt von blutsverwandten Eltern (s. Abb.2) geboren wurde, begann in typischer Weise im 8. Monat mit unstillbarem Erbrechen, Nahrungsverweigerung und einer auffallenden Polydypsie. Durch den verdächtigen Urinbefund und rachitische — Vit.-D-resistente — Knochenveränderungen wurde nachdrücklich auf den Komplex der renalen Rachitis verwiesen. Um die bei „renal rickets" nicht seltenen Anomalien der ableitenden Harnwege auszuschliessen, wurde ein retrogrades Pyelogramm angefertigt und bei normalen Ausscheidungsverhältnissen, mühelosem Ureterenkatheterismus zarte, wohlgeformte Nierenbecken gefunden. Bemerkenswert war, dass mit der weiteren Verschiebung des Ca/P-Quotienten im Serum ein positives Facialisphänomen auftrat und bei unverändert sauerer Urinreaktion keine reduzierenden Substanzen ausgeschieden wurden. Mit der im Röntgenbild

verfolgbaren Ausheilung der Rachitis (ohne jede Vigantoltherapie!) trat unter Normalisierung der Kalk-Phosphor-Relation des Blutes ein plötzlicher Umschlag in Urinalkalose und zugleich eine „Glykosurie" auf. Während der klinischen Beobachtung wurden in unregelmässigen Intervallen wechselnde Temperaturen registriert, die anfangs als Durstfieber gedeutet, aber weder durch Flüssigkeitszufuhr noch durch Penicillin beeinflusst werden konnten. Mit einem langsamen, aber beständigen Abfall des Körpergewichtes wurde mehrfach eine beträchtliche Erhöhung des Rest-N gemessen, Blutzucker, Phosphatase, Harnstoff, Chloride, Chlolesterin z. T. in abweichenden Konzentrationen gefunden, Ergebnisse, die gemeinsam mit den ermittelten Urinwerten in einer Übersicht zusammengefasst sind.

Tabelle 1.

Blut			Urin		
Rest–N bis	71	mg%	Gesamtphosphor	11,4	mg%
Eiweiss	6,9	g%	Harnstoff	0,9	g%
Indikan	0,34	mg%	Chloride	877	mg%
Chloride	334	"	Cystin } im Sediment nicht		
Blutzucker	84	"	Leucin } nachweisbar		
Calcium	6,55	"	Amino–N	zwischen 72–284	mg%
Phosphor (anorg.)	7,15	"	Cystin	zwischen 280–340	"
Phosphatase	25,5	K.A.E.	Bence–Jones		neg.
Harnstoff	96	mg%	Sulkowitsch		"
Cholesterin	347	"	Millon	roter Schaum	
Cystin	19,5	"	Benedict		grün
Glutaminsäure	23,4	"	Fe Cl_3		neg.

Im vorliegenden Falle ist durch die mit einer Verschiebung des Ca/P-Quotienten aufgetretenen Knochenveränderungen innerhalb des bekannten Manifestationsalters der Verdacht einer Aminoacidurie mit Cystinspeicherung geweckt worden. Zur Bestätigung des begründeten Verdachtes wurde eine Spaltlampenuntersuchung der Cornea durchgeführt. Hierbei fanden sich die für die infantile Cystinose beweisenden „kristallstaubähnlichen Einlagerungen", welche subepithelial liegen, aus feinsten Pünkt-

chen zusammengesetzt sind und dem bei blosser Betrachtung unverdächtigem Auge eine leichte bräunlich schillernde Trübung verliehen.

Durch diesen Befund veranlasst, entnahmen wir in Zusammenarbeit mit ULLERICH im Lachgasrausch mit einem Scherenschlag ein Stückchen Bindehaut aus der unteren Umschlagfalte des Conjunktivalsackes, breiteten das Gewebestückchen nach Art eines Zupfpräparates auf einem Objektträger aus und sahen ohne jede Färbung bei mittelstarker Vergrösserung eine Menge Kristalle in unregelmässiger Verteilung, in Bündeln zusammengerafft oder verstreut innerhalb der noch eben erkennbaren Gewebsstruktur der Conjunktivalhaut (Abb. 3). Morphologisch lassen sich scharf konturierte hexagonale Kristalle von stabförmigen Elementen verschiedener Grösse unterscheiden, wobei letztere parallel zur Basis gelegene Bruchlinien aufweisen. Daneben tauchen spitzpyramidale Nadeln auf, die in Bündelform angeordnet sind (Abb. 6) und zufolge ihrer feineren Struktur gegenüber den plumperen Rechteckformen an eine andere Kristallformation denken lassen. Diese Vermutung wird durch Eigentümlichkeiten der Lichtbrechung gestützt, indem sich nachweisen lässt, dass die für Cystin beweisenden tafeligen Sechsecke als auch die stängigen Rechtecke übereinstimmend negativ doppelbrechenden Charakter haben, während die Analyse der feineren Kristallnadeln positive Doppelbrechung zeigt. Die genauere Differenzierung der Tracht erlaubt beide Kristallformationen verschiedenen Klassen zuzuordnen, wobei hexagonal haloedrische (D_{6h}) von hexagonal hemimorphen (C_6) Kristallen unterschieden werden können. Verzwilligung kann an keiner Stelle nachgewiesen werden; die Lichtbrechung der Kristalle ist höher als die des umgebenden Mediums.

Die Darstellung der Kristalle in der Conjunktivalhaut scheint

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Abb. 3. Verschiedene Kristallformationen in einem Gewebsstückchen der Conjunktiva (untere Umschlagfalte) bei einer Vergrösserung von 1:800. Ausser stängigen Rechteckformen finden sich die für Cystin beweisenden hexagonalen Tafeln neben büschelförmig angeordneten Nadeln.

Abb. 4. Kristalldarstellung in der excidierten Augenbindehaut im polarisierten Licht, wobei sich morphologisch verschiedene Strukturen (mit differierenden Eigenschaften der Lichtbrechung) abgrenzen lassen. Abb. 5. Ausschnittsvergrösserung der Abb. 5, in der vorwiegend solche Substanzen erfasst sind, die – wie Cystin – negativ doppelbrechenden Charakter haben.

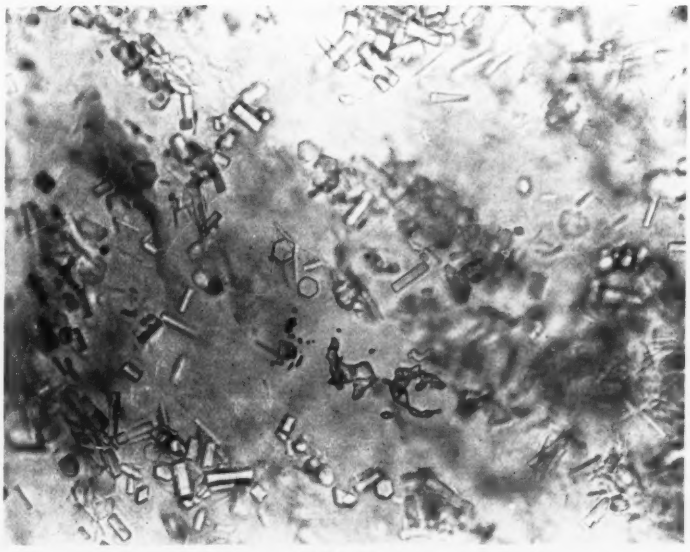

Abb. 3.

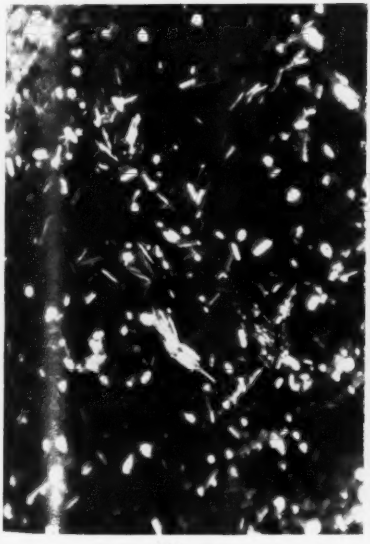

Abb. 4.

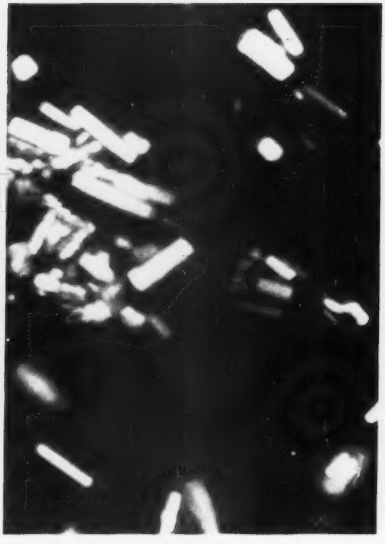

Abb. 5.

Abb. 6. Kristalldarstellung bei Cornealcystinose im polarisierten Licht. Aus schnittvergrösserung mit spitzpyramidalen Nadeln, die entgegen den plumperen Rechteckformen und hexagonalen Tafeln eine positive Doppelbrechung ergeben.

mir in Anbetracht der einfachen Handhabe eine für Klinik und Praxis gleich brauchbare Methode zu sein, mit deren Hilfe es leicht gelingt, die Verdachtsdiagnose „Cystinspeicherkrankheit" zu objektivieren. Die nicht unerheblichen Schwierigkeiten, die über den Umweg blutchemischer Untersuchungen und papierchromatographischer Differenzierungen zur Diagnose der Aminoacidurie mit Cystinspeicherung führen, werden durch den direkten Kristallnachweis im Gewebe erheblich vereinfacht.

Bestehen Zweifel an der Kristallnatur der in der Bindehaut eingelagerten Elemente, so gelingt es schnell mit polarisiertem Licht doppelbrechende, scharf konturierte, gelegentlich hexagonale Prismen verschiedener Grösse in der homologen durch die Polaris-

tion ausgelöschten Gewebsstruktur darzustellen (Abb. 4, 5). Es bedarf der Erwähnung, dass die Fülle der hier aufleuchtenden Kristalle kaum einen Vergleich mit denen des Sternalmarkes zulässt. Um einer Verwechselung mit anderen Kristallformationen zu entgehen — das Auftreten eines Kristallstaubphänomens ist für den Ophthalmologen ein durchaus ungewöhnliches Ereignis — so besteht ausser dem chemischen Cystinnachweis in kleinen Gewebsstückchen die Möglichkeit durch Röntgenspektrographie eine genaue Differenzierung und Bestimmung durchzuführen.

Am postmortal enukleierten Auge eines cystinspeicherkranken Kindes hat BÜRKI den spezifischen Cystinnachweis durch biochemische Reagenzien führen können (Nitroprussid-Natrium-Cyanid-Reaktion nach BRAND, HARRIS u. BILOON) und eine Verwechselung mit anderen Speichersubstanzen, insbesondere Harnsäurekristallen, sichergestellt, obgleich kristallographisch eine sichere Unterscheidung keine Schwierigkeiten macht.

In einer älteren Mitteilung hat ESSER (1941) den Nachweis der Cystinkristalle im Sternalpunktat für die Diagnose der Cystinspeicherkrankheit hervorgehoben. Ausser den hierfür erforderlichen Hilfsmitteln ist das Anfertigen von Knochenmarksausstrichen zeitraubend, mit Sicherheit aber das Auffinden von doppelbrechenden Kristallen — zumal dann, wenn kein polarisiertes Licht zu Verfügung steht — weit schwieriger, als in der Augenbindehaut. Wir haben gleichfalls Ausstriche von Sternalpunktaten durchsucht, gelangen aber zu dem Schluss, dass nur in besonders dicken Ausstrichen ein Suchen nach kristallinischem Cystin lohnt, in vielen Fällen aber ergebnislos verläuft, weil das ungeschulte Auge des Nachuntersuchers die Kristallformen, welche am besten in den Randpartien darzustellen sind, übersieht. Für Sternalmark- wie Bindehautuntersuchungen gilt der Hinweis, dass die gewonnenen Praeparate nur mit hochprozentigen alkoholischen Lösungen fixiert werden können, da mit saueren Farbstoffen und käuflichem Formalin das Cystin gelöst wird, ein Umstand, an dem in früheren Jahren manche Untersucher gescheitert sind.

Von gleich grosser Bedeutung ist für die Diagnose der Cystinspeicherkrankheit der Nachweis der AS-Ausscheidung im Urin,

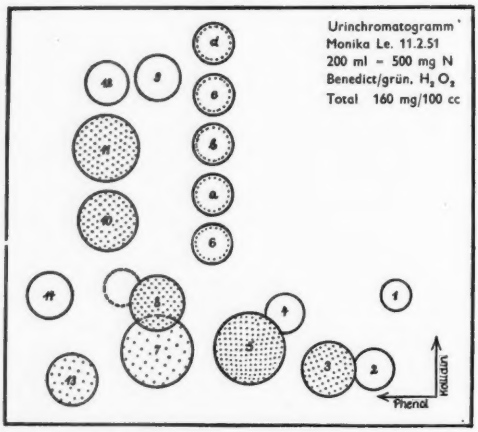

Abb. 7. Schematische Darstellung eines zweidimensionalen (Phenol-Kollidin) Chromatogrammes des Urins bei Aminoacidurie vom Cystinosetyp.

1 Cystin (nach Oxydierung zu Cystein mit H_2O_2) ..... ~ 1 mg/100 cc
2 Aspartinsäure ..... ~ 2 mg/100 cc
3 Glutaminsäure .... ~ 10 mg/100 cc
4 Serin ..... ~ 5 mg/100 cc
5 Glycin ..... ~ 30 mg/100 cc
6 (a—d) Testaurin .. 5–40 mg
7 Glutamin ..... ~ 15 mg/100 cc
8 Alanin ..... 20 mg/100 cc
9 Tyrosin ..... ~ 2 mg/100 cc
10 Valin ..... ~ 15 mg/100 cc
11 Leucin ..... ~ 20 mg/100 cc
12 Phenylanalin .... ~ 7,5 mg/100 cc
13 Lysin ..... ~ 20 mg/100 cc
14 Prolin (gelb +++) ~ 15 mg/100 cc

welche in befriedigender und eleganter Weise durch die Papierchromatographie (CONSDEN, GORDON, MARTIN, 1944) erfasst werden kann. Die Tatsache, dass sich das Urincystin bei cystinspeicherkranken Kindern verlässlicher Darstellung entzieht, dagegen bei der harmlosen Stoffwechselanomalie der Cystinurie leicht nachgewiesen werden kann, veranlasste uns, auf die Aminosäurenkonzentration des Urins bei der Cystinose einzugehen. Aus genaueren Differenzierungen mit Hilfe von zweidimensionalen Papierchromatogrammen, deren Anfertigung wir Dr. Bickel (Birmingham) verdanken, lässt sich ersehen, dass hier vor allem Lysin, Alanin und Leucin den Rahmen der physiologischen Ausscheidungsraten übersteigt. Die grobquantitative Auswertung ergibt gegenüber Normalwerten eine um das 3—5 fach vermehrte Exkretion (Abb. 7). Obgleich die Eigenarten des chromatogra-

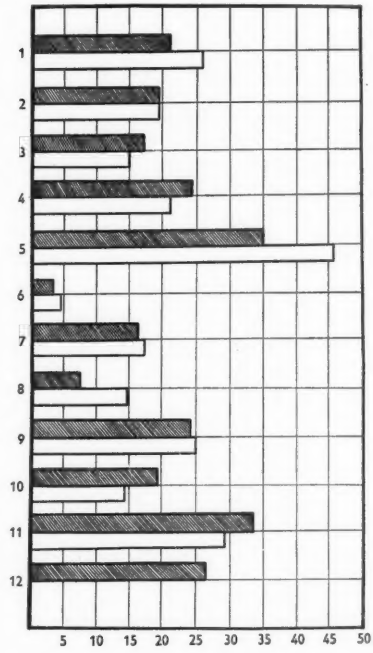

Abb. 8. Serumkonzentrationen verschiedener freier Aminosäuren bei der Cystinspeicherkrankheit nach mikrobiologischer Bestimmung. Die schraffierten Säulen stellen normale Durchschnittswerte gesunder Kinder, die hellen Säulen die Abweichungen bei der Cystinose dar. Normaler Cystinwert (2), pathologisch erhöhte Arginin- (1) und Lysin- (5) Konzentration. (Rest–N des Besimmungstages 56 mg%.)

1 Arginin, 2 Cystin, 3 Isoleucin, 4 Leucin, 5 Lysin, 6 Methionin, 7 Phenylanalin, 8 Tryptophan, 9 Treonin, 10 Tyrosin, 11 Valin, 12 Glykokoll.

phischen Bildes in jedem Falle ein für die chronische Aminoacidurie vom Cystinosetyp charakteristisches Muster zeigt, handelt es sich hierbei um eine qualitative Bestimmung, die durch quantitative Analyse und Ermittelung der Amino-N-Fraktionen des Urins näher begrenzt und ergänzt werden sollte. Genauere Erhebungen, für die wir Dr. TEPE aus dem physiologisch-chemischen Institut der Universität Hamburg (Dir. Prof. Dr. KÜHNAU) zu besonderem Dank verpflichtet sind, lassen eine eindeutige Erhöhung der Amino-

-N-Werte des Urins erkennen, die in bindender Abhängigkeit von der Tagesurinmenge den aus der Literatur über das DEBRÉ-de TONI-FANCONI-Syndrom bekannt gewordenen Konzentrationen (DENT) entsprechen. Nach PETERS u. VAN SLYKE beläuft sich die normale Amino-N-Ausscheidung auf 1—2 %, nach neueren Angaben von ALBANESE auf 2,2—4,5 % des Gesamtharnstoffes. Einzelheiten dieser Untersuchungen werden im Zusammenhang mit Serumanalysen der Cystinspeicherkrankheit an anderer Stelle niedergelegt (4).

Von besonderer Bedeutung und für die pathogenetische Deutung dieses Syndroms wesentlich sind die noch wenig erforschten Aminosäurenkonzentrationen des Blutes. Die bisher vorliegenden Ergebnisse sind unterschiedlich und nicht umfassend genug, um Bindendes über die praeranale Konzentration der AS, insonderheit des Cystins, aussagen zu können. Dem wiederholt normal befundenen As-Spiegel des Blutes bei Aminoacidurie (STOWERS, DENT, FANCONI) möchten wir neue mit mikrobiologischen Methoden verarbeitete Serumuntersuchungen gegenüberstellen (Abb. 8), für deren Durchführung wir Dr. SCHREIER (Heidelberg) besonderen Dank schulden. Hierbei ergab sich unter gleichzeitiger Aufstellung von Standartkurven und parallel laufenden Normalurinen eine signifikante Erhöhung des Lysins und ferner physiologische Konzentrationen übersteigende Arginin-, Tryptophan- und Phenylanalinwerte (s. Tabelle 2). Bemerkenswert erscheint, dass im Serum des cystinspeicherkranken Kindes keine Cystinvermehrung nachzuweisen war. Damit scheint die Vorstellung des „praerenalen oberflow" entkräftet zu werden.

Durch die Anwesenheit SH-haltiger Verbindungen im Blute und ihre Anhäufung in den Ausscheidungsorganen werden bestimmte Beziehungen zum Zuckerhaushalt nahegelegt. Die Glukosenatur der bei Aminoacidurie mit Cystinspeicherung ausgeschiedenen Substanzen kann nicht als erwiesen angesehen werden, zumal SH-haltige Aminosäuren für den gelegentlichen positiven Ausfall der Reduktionsproben bei dieser Erkrankung angeschuldigt wurden (HOTTINGER). Es muss ferner als ein bemerkenswertes Charakteristikum angesehen werden, dass bei der Cystinspeicherkrankheit eine Glykolabilität besteht und auf Zucker-

Tabelle 2.

Urinkonzentrationen verschiedener Aminosäuren bei Aminoacidurie vom Cystinosetyp. Einzelwerte (I–III) und Durchschnittswert (A) aus Nüchternurinportionen von 3 aufeinanderfolgenden Tagen, die mit mikrobiologischen Methoden ermittelt wurden und dem errechneten Durchschnitt (B) bekannter Grenzwerte gesunder Kinder (nach SCHREIER) gegenübergestellt sind. Dabei ergibt sich ein normaler Cystinwert und für Leucin und Lysin eine ausserhalb der Streubreite liegende Erhöhung.

Aminosäuren	I	II	III	A	B
Arginin	3,4	4,2	4,3	3,9	14
Cystin	28	—	34	31	35
Isoleucin	0,9	0,4	0,4	0,5	3,8
Leucin	10,8	8,5	9,5	9,6	4,2
Lysin	11,7	14,7	15,6	14	9,5
Methionin	0,7	0,4	0,4	0,5	2,1
Phenylanalin	2,1	5,0	4,7	3,9	1,5
Tryptophan	5,4	4,3	8,6	6,1	8,5
Threonin in	5,7	5,1	8,4	6,4	9,5
Tyrosin	3,8	4,2	7,4	5,1	8,5
Valin	2,4	2,6	3,0	2,6	9,5

belastungen toxische Zustandsbilder beobachtet wurden (DEBRÉ, FANCONI). Während in vielen Fällen Glukose als eine die Reduktionsproben beeinflussende Substanz nachgewiesen wurde (LIGNAC, VAN CREVELD, BICKEL u. a.), sahen wir in einigen Urinproben unseres Kindes wechselnden Ausfall der Zuckerproben, keine typische Zuckerpolarisation und auch die entscheidenden Gärproben negativ verlaufen. In einem eindimensionalen Zucker-Chromatogramm stellte sich dagegen Glukose mit einer reinen Testlösung in gleicher Höhe dar.

Seltsamerweise wird trotz der pathologischen Zuckerbelastungskurven und der Adrenalinempfindlichkeit keine Hyperglykämie (eher Tendenz zu Hypoglykämie) gefunden, womit die Vermutung bekräftigt wird, dass möglicherweise der für die Zuckerrückresorption und Exkretion verantwortliche tubuläre Nierenabschnitt derart geschädigt ist, dass die Nierenschwelle für Glukose erheb-

lich gesenkt wird. Diese Ereignisse werden auf eine Phosphorilierungs- und Phosphatasehemmung im Bereiche der Nierentubuli bezogen und durch den Befund von STOWERS, DENT u. CAMERON, die durch Phosphatasefärbung nach GONIERI in der Tat ein eindeutiges Fehlen dieses Fermentes in den proximalen Nierentubulusabschnitten nachwiesen, eindrucksvoll unterstrichen. Die Vermutung, dass durch S-haltige Verbindungen im Blute Zuckerhaushalt und Körpertemperatur beeinflusst werden, haben wir durch eigene tierexperimentelle Untersuchungen erweisen können und wahrscheinlich gemacht, dass die Schwefelanreicherung im Blute zu einer Hyperglykämie und zu Temperaturanstieg führt (WEYERS, 1947). BRUNS u. RUMMEL haben die Stoffwechselwirkung von Cystein und SH-Gluthation in pharmakologischen Konzentrationen untersucht, um die Wirkung von Cystein am geschlossenen Fermentkomplex der Zelle in vitro nachzuweisen. Dabei zeigte sich, dass Cystein den Sauerstoffverbrauch und die Kohlensäurebildung um mehr als 100 % erhöht. Anorganisches Phosphat wird in einem erheblichem Ausmass in Esterbindung überführt (bis zu 20 mg %/2 St.). Das Substrat dieser Oxydationsvorgänge ist Glukose.

Wissenswert erschien uns in diesem Zusammenhang das Ergebnis einer vorsichtigen Zuckerbelastung, die wir mit Hilfe von stündlich 7 g Dextrose durchführten, um abschliessend den Adrenalineffekt zu prüfen. Erstaunlicherweise ergab hierbei die stündliche Blutzuckerbestimmung und ihre graphische Darstellung einen paradoxen Kurvenverlauf mit einem Abfall nach Dextrosegaben und steilem Anstieg nach Adrenalininjektion, Verhältnisse, die man bei Leberschäden zu sehen gewohnt ist. Der fehlende STAUB-Effekt in Verbindung mit der starken TRAUGOTT-Reaktion weisen mit weiteren Differenzierungen des Elektrophoresediagrammes auf eine hepatogene Mitbeteiligung hin (s. u.).

Von den abweichenden Reaktionen nach Glukosebelastungen ausgehend ist BICKEL Verschiebungen des Kaliumhaushaltes dieser Erkrankung nachgegangen, da einige Züge im Erscheinungsbild der chronischen Aminoacidurie, die besonders bei Stoffwechselkrisen dieser Erkrankung in Erscheinung treten, durch eine Störung der extra- und intracellulären Kaliumbilanz erklärt

werden können. Nach persönlicher Mitteilung hat BICKEL derartige Erhebungen an cystinspeicherkranken Kindern durchführen können und gefunden, dass nach Zuckerbelastungen ein steiler Abfall der Blutkaliumwerte zu verzeichnen ist und — bei konstanter Alkalireserve — die verlorengegangene Kaliummenge im Urin wiedergefunden werden kann. Die nach Zuckerzufuhr erzielte Hypokaliämie ging mit einer Diuresesteigerung einher.

Durch signifikante Erniedrigung des Blutkaliumspiegels werden EKG-Veränderungen ausgelöst (allerdings nicht ohne Verwechselungsmöglichkeit mit gleichen Zustandsbildern anderer Ätiologie) die gleichfalls für die Diagnose des FANCONI-Syndroms brauchbare Hinweise zu liefern vermögen. Bei K-Mangel im Serum wird ein Niederspannungs-EKG, eine verbreiterte T-Zacke, zuweilen Extrasystolen und Umkehrungen der Nachschwankungen beobachtet. Wir haben nach mehrfachen EKG-Kontrollen bei chronischer Aminoacidurie vom Cystinosetyp Andeutungen einer LOW-Voltage, Verlängerung der Q-T-Strecke, besonders hohe und breite T-Zacken ohne Inversion gesehen, betonen aber, dass wir ausgesprochene Stoffwechselkrisen, wie sie dem DEBRÉ-de TONI-FANCONI-Syndrom eigen sind, während der klinischen Behandlung nicht erlebt haben.

Mit der Muskelhypotonie, Hydrolabilität, Erbrechen und Infektneigung erinnern manche Züge dieser Erkrankung — auch in psychischer Hinsicht — an die Coeliakie. In diesem Zusammenhang will es mir nicht unbedeutend erscheinen, dass mehrfach Kinder mit Cystinose und Steatorrhoe vergesellschaftet gesehen wurden und auch WALLGREN bei Aminoacidurie auf dem Höhepunkt der AS-Ausscheidung eine Verschlechterung der Fettresorption durch den Darm beobachten konnte.

Es mag hier angemerkt werden, dass auch die Coeliakie Phosphatasehemmung und Resorptionsstörungen mit Entkalkungsosteopathie, Osteoporose sowie Auswirkungen auf die Körperwachstumssphäre zeigt, ein Mechanismus, der nicht nur für das Kindesalter sondern auch für Erwachsene (Sprue) Gültigkeit besitzt. Die bei „Celiac disease" (GEE, 1888) erfolgversprechende Nebennierenrindentherapie scheint aber nach bisherigen Erfah-

Tabelle 3.

Elektrophoreseuntersuchungen bei Cystinspeicherkrankheit.

Serumeiweisse (Elektrophor.)	Albumine	Globuline		
		α	β	γ
Cystinspeicherkrankheit im Alter von 1 Jahr	48 %	20,1 %	16,5 %	14,5 %
Einjähriges gesundes Kind (Vergleichswerte)	63 %	12 %	12,7 %	11,5 %

rungen die Phosphorilierungsvorgänge der chronischen Aminoacidurie nicht zu bessern (FANCONI).

Als Sitz der Speicherung ist für die Cystinose das Mesenchym, besonders das Retikulo-Endotheliale System angesehen worden (BÜRKI, BICKEL u. BAAR). LINNEWEH glaubt auf Grund des Fehlens von Veränderungen im Elektrophoresediagramm nach eigenen Untersuchungen dieser Vorstellung nicht folgen zu können. Diese Unstimmigkeiten haben uns bewogen, die Frage aufzugreifen und mit der von TISELIUS entwickelten Methode zunächst Normalwerte bei einem gesunden gleichaltrigen Vergleichskind zu ermitteln und diese den bei chronischer Aminoacidurie mit Cystinspeicherung gefundenen Abweichungen der Bluteiweisskörper gegenüberzustellen (s. Tabelle 3).

Eine Kontrolluntersuchung mit der papierchromatographischen Bestimmungsmethode nach WIELAND hat fast übereinstimmende Grössen der Albumine, alfa-, betha- und gamma-Globuline ergeben. Die Untersuchungsergebnisse verdeutlichen eine Abnahme der feindispersen Albumine unter Zunahme der grobdispersen Globuline. Auffallend ist eine Vermehrung der alfa- und betha-Globuline. Ob allerdings die Verschiebung des Albumin-Globulin-Quotienten mit der Cystinspeicherung in unmittelbare Beziehung gebracht werden kann, erscheint fraglich, wenn man die Untersuchung von WALLGREN berücksichtigt, der bei einem zweijährigen Knaben mit Aminoacidurie *ohne* Cystinspeicherung als bemerkenswerten Befund gleichfalls eine Globulinvermehrung im Serum

hervorhebt. WALLGREN möchte diesen Befund auf eine hepatogene Funktionsstörung beziehen. Uns haben gleiche Vorstellungen bewogen, mit Hilfe von Leberfunktionsproben (Salzsäure-Kollargol-Reaktion, Thymoltrübungstest) eine Leber-mitbeteiligung zu eruieren, jedoch baben wir keine positiven Ausfälle gesehen. Die Bewertung solcher Stabilitätsproben hat jedoch eine Albuminverminderung weitgehend zu berücksichtigen, da letztere das Ergebnis der Leberfunktionsteste massgeblich beeinflussen. WUHRMANN u. WUNDERLY fanden mehrfach negative Leberfunktionsproben in Fällen von Hypalbuminämie, wo nach dem klinischen Bild der Test hätte pos. ausfallen müssen. Hierzu ist anzumerken, dass ein pos. Takata-, oder Thymoltrübungstest auf eine vermehrte Aussalzung der Serumproteine zu den leichteren Phasen hin zurückzuführen ist und — wie in unserem Falle — mit einer Vermehrung der Gesamtglobuline vergesellschaftet ist.

Bereits die Abnahme des Blutkalziums ist an eine Eiweissverminderung gebunden, da eine echte Kolloidbindung des Kalziums an Eiweiss angenommen wird. Die in unserem Falle durch das Vorliegen einer hypalbuminämischen Hypokalciämie gestützte Anschauung erklärt zugleich den konstatierten EKG-Befund einer verlängerten Q-T-Zeit. In diesem Zusammenhang bedarf ferner ausdrücklicher Erwähnung, dass die elektrophoretisch differenzierte Dysproteinämie auch für die Hypercholesterinämie — wie sie mehrfach bei Cystinspeicherkrankheit mitgeteilt wurde — eine hinreichende Erklärung gestattet, wenn man berücksichtigt, dass α und β Globuline als Träger der Lipoidproteine mit ihrem Anstieg einen erhöhten Cholesterinwert verständlich erscheinen lassen.

Pathogenetisch lassen sich für die Cystinspeicherkrankheit enge Beziehungen zu Stoffwechselkrankeiten nachweisen, die dem Komplex der renal bedingten Resorptionsstörungen angehören, aber selbst keine Nierenerkrankungen darstellen. In erster Linie seien die variablen, dem MILKMAN-Syndrom zuzuordnenden Krankheitsbilder bei Kindern (EWERBECK, KOSENOW u. a.) und Erwachsenen (MILKMAN, BARGMANN, FRANK u. a.) angeführt. Bei diesen renal bedingten Entkalkungsosteopathien handelt es sich immer um Kalk-Phosphorstörungen, die wie Osteomalacien anderer Genese symmetrische Umbauzonen der

langen Röhrenknochen (LOOSER) bewirken. Die durch verschiedene Ursachen entstehenden Mineralverschiebungen, die zu gleichen morphologischen Knochenbildern führen, streng zu trennen, wie es HEROLD vorgeschlagen hat, erscheint wenig aussichtsreich, da anatomische, histologische, radiologische und klinische Untersuchungen die Vit.-D-Mangel-Rachitis von renal bedingten Rachitiden nicht sicher zu unterscheiden vermögen.

Die Differenzialdiagnose der Cystinspeicherkrankheit hat neben der Vit.-D-resistenten renalen Rachitis (FANCONI u. CHASTONAY, WALLGREN u. a.) die D-Hypervitaminose zu berücksichtigen. Der Ausfall der SULKOWITCH'schen Probe kann eine rasche Entscheidung herbeiführen, indem bei D-Hypervitaminose mit 2 cm³ des Sulkowitch'schen Reagens zu 5 cm³ Urin eine grobwolkige Trübung entsteht, die bei chronischer Aminoacidurie mit leicht wolkiger Trübung negativ ausfällt. Ex iuvantibus ergeben sich weitere Hinweise, da nach dem Aussetzen der Vitamin D-Zufuhr die Hyperkalciämie und die der Cystinose vergleichbaren klinischen Erscheinungen zu schwinden pflegen.

Die Nephrocalcinosis (LIGHTWOOD-ALBRIGHT) mit Insuffizienz des distalen Tubulusabschnittes (Isostenurie, Urinakalose, Blutacidose usw.) kann wie die chronische Cystopyelitis bzw. Nierenmissbildung differentialdiagnostische Schwierigkeiten machen. An das seltene Bild der „Lebercirrhose mit frühinfantilem Zwergwuchs und hypophosphatämischer Rachitis" („Rachitis hepatica"), ECKSTEIN 1950, ist besonders wegen der bei Lebercirrhose auftretenden Aminoacidurie und Glykosurie zu denken. Von Seiten der Speicherungssymptone weist schliesslich der von FANCONI u. BICKEL (1946) mitgeteilte Fall (II) einer Glykogenose mit Aminoacidurie in dieselbe Richtung. Auf die in diesem Zusammenhang interessante Phänokopie der PFAUNDLER-HURLER'schen Krankheit durch die Cystindiathese hat ULLRICH (1948) in Verbindung mit erbbiologischen Erwägungen hingewiesen.

Zusammenfassung

1. An Hand einer neuen Beobachtung von chronischer Aminoacidurie mit Cystinspeicherung, welche in typischer Weise ein blondhaariges 1-jähriges Mädchen blutsverwandter Eltern betrifft, werden neue diagnostische und klinische Befunde dieser seltenen Erkrankung zusammengestellt.

2. Neben der älteren Methode des Cystinkristallnachweises im Sternalmarkausstrich vermag eine technisch einfache Darstellung des kristallinischen Cystins in der Augenbindehaut die Verdachtsdiagnose schnell zu sichern. Kristallographische Differenzierungen erlauben hierbei grundsätzlich 2 Kristallformationen zu unterscheiden, die durch Eigentümlichkeiten der Lichtbrechung voneinander abweichen.

3. Chromatographische Aminosäurenbestimmungen werden mikrobiologisch ermittelten AS-Konzentrationen des Urins und den bislang wenig bekannten Serumwerten gegenübergestellt. Dabei lässt sich feststellen, dass neben wechselnden Konzentrationen anderer Aminosäuren weder im Serum noch im Urin eine Cystinvermehrung vorhanden ist.

4. Die Speicherung des schwerlöslichen Cystins im Retikulo-endothelialen System kann durch den Nachweis von Verschiebungen der Serum-eiweisskörper nach elektrophoretischer Bestimmung bekräftigt werden.

5. Bezüglich der Glykolabilität dieser Erkrankung werden neue mit dem Zuckerhaushalt gekoppelte Verschiebungen der Kaliumbilanz angeführt. Die Glukosenatur der, durch Anhäufung S-haltiger Verbindungen im Blute der an Cystinose erkrankten Kinder, erklärbaren Ausscheidung reduzierender Substanzen wird durch chromatographische Differenzierungen sichergestellt.

6. Mit den kurz erwähnten pathogenetisch nahestehenden Zustandsbildern wird vor allem eine Verwandtschaft der Aminoacidurie vom Cystinosetyp mit der Coeliakie hervorgehoben und auf die Differenzialdiagnose eingegangen.

Nouvelles données sur le diagnostic et la clinique de l'aminoacidurie chronique avec dépôt de cystine.

A la lumière d'une nouvelle observation d'amino-acidurie chronique, avec dépôt de cystine, survenue chez une petite fille de 1 an, aux cheveux blonds, née de parents consanguins, on rapporte des données nouvelles concernant le diagnostic et la clinique de cette rare maladie. Outre l'ancienne méthode d'identification des cristaux de cystine dans la ponction sternale, un diagnostic douteux peut être confirmé rapidement par une méthode technique simple, mettant en évidence des cristaux de cystine, au niveau de la conjonctive. La différenciation cristallographique permet ici de distinguer essentiellement deux formes de cristaux, qui diffèrent

par une déviation spécifique de la lumière. La détermination chromatographique des acides aminés s'oppose à leurs concentrations, découvertes microbiologiquement dans les urines, et aux valeurs du sérum peu connues jusqu'ici. De plus, on peut assurer, qu'à côté des concentrations variables des autres acides aminés, il n'existe aucune augmentation de cystine, ni dans le sérum, ni dans l'urine. Le dépôt de cystine, difficile à dissocier, dans le système réticulo-endothélial, peut être confirmé par l'examen des modifications de l'albumine sérique, par la méthode electrophorétique. En ce qui concerne la glycolabilité de cette maladie, on rapporte de nouvelles modifications du bilan du potassium, couplées avec le métabolisme du sucre. Les enfants atteints de cystinose ont par une accumulation de liaisons soufrées dans le sang, une excrétion de substances réduites: la nature du glucose de ces dernières peut-être confirmée par différenciation chromatographique. Une courte mention des états pathogéniques voisins souligne, avant tout, une parenté entre l'amino-acidurie de type cystinose et la maladie coeliaque.

New Studies on the Diagnosis and Clinic of Chronic Aminoaciduria with Storage of Cystine.

Latest observations of a typical chronical aminoaciduria with storage of cystine in the 1 year old, fair-haired daughter of parents related to each other have led to new diagnostic and clinical findings concerning this rare disease. Besides the older method of proving the presence of cystine crystals in smear preparations from the sternal marrow, the technically simple preparation of crystalline cystine in the conjunctiva of the eye can be used to confirm a suspected diagnosis. In crystallographic differentiation two kinds of crystal formation may be distinguished, differing from each other by a characteristic refraction. Chromatographic estimations of amino acids are compared with microbiologically ascertained concentrations of amino acids in the urine and with the less known serum estimations. It may be stated that although there are varying concentrations of other amino acids there is no increase of cystine in either serum or urine. The storage of the almost insoluble cystine in the reticuloendothelial system is confirmed by electrophoretic estimation, proving that a transposition of serum proteins has taken place. As far as the glycose lability of this disease is concerned, new transpositions of the potassium balance connected with the metabolism of glucose are discussed. It is doubtful whether the excretion of reducing substances which could be explained by the accumulation of acid compounds in the blood of children suffering from cystinosis is of the glucose kind, since there is discrepancy between polarimetry and decisive fermentation tests. Special emphasis is placed on the close affinity between aminoaciduria of the cystinosis type and celiac disease. This is based on the similar pathogenesis and clinical picture.

Nuevas investigaciones para el diagnóstico y cuadro clínico de la aminoaciduria crónica con almacenamiento de cistina.

A propósito de una nueva observación de aminoaciduria crónica con almacenamiento de cistina realizada en una niña de un año hija de padres consanguíneos se resumen nuevos procedimientos para el diagnóstico y clínica de esta rara afección. Al lado de los métodos antiguos de investigación de los cristales de cistina en la médula ósea de la punción esternal se detalla una técnica de diagnóstico rápido por la investigación de cristales de cistina en la conjuntiva ocular. La diferenciación cristalográfica permite aquí fundamentalmente separar 2 formaciones de cristales identificables por las diferencias de refracción de la luz. Se confrontan los valores de las determinaciones cromatográficas de aminoacidos con los valores de concentración de aminoácidos en la orina determinados por métodos microbiológicos. Se comprueba que junto a valores variables en la concentración de aminoádicos en suero y en orina hay valores elevados de cistina. El almacenamiento de los cristales insolubles de cistina en el sistema reticuloendotelial puede comprobarse junto a la desviación de los cuerpos albuminoideos por determinación electroforética. Referenta a la glicolabilidad existente en esta enfermedad han podido encontrarse alteraciones respecto al balance de potasio. Por diferenciación cromatográfica se ha podido estudiar la naturaleza de las sustancias reductoras eliminadas por los niños enfermos de cistinosis como de naturaleza glucosida. Se establece parentesco a través del conjunto clínico y patógenico con la aminoaciduria del tipo cistinosis y la celíaca.

Literaturnachweis

Baar u. Bickel: Kongressberichte der 50. Tagung Dtsch. Gesellsch. Kinderheilk. Lübeck 1950.

Bargmann: Entkalkungsosteopathien bei Niereninsuffizienz. Berl. med. Zschr. 1 1950.

Bickel: persönliche Mitteilung.

Boehncke, Weyers u. Tepe: Beobachtungen bei Cystinspeicherkrankheit (im Druck Z. Kinderheilk.)

Bruns u. Rummel: Stoffwechselwirkungen von Cystein und Gluthation. Klin. Wschr. *29:* 62, 1951.

Bürki: 1. Über Augenveränderungen bei der Cystinkrankheit. Ann. Paediat. *156*: 324 1941. — 2. Über die Cystinkrankheit im Kleinkindesalter unter besonderer Berücksichtigung des Augenbefundes. Ophtalmologica, *101*: 257 u. 331, 1941.

Consden, Gorden u. Martin: Qualitative Analysis of Proteine: A Partition Chromatographic Method. J. Biochem. *38:* 224, 1944.

Dent: Der Aminosäurestoffwechsel. Schweiz. med. Wschr. *80:* 752, 1950.

Ecestein: Lebercirrhose mit frühinfantilem Zwergwuchs und hypophosphatämischer Rachitis. Ann. Paediat. Vol. *174:* 3, 1950.

Esser: Zur Diagnose der Cystinkrankheit. Ann. Paediat. 156*:* 34, 1941.

Ewerbeck: Ein Milkman-Syndrom im Säuglingsalter. Z. Kinderheilk. *67:* 566, 1950.

Fanconi: 1. Der frühinfantile nephrotisch-glycosurische Zwergwuchs mit hypophosphatämischer Rachitis. Jb. Kinderheilk. *147:* 299, 1936. — 2. Neue Aspekte der Nierenpathologie. Schweiz. med. Wschr. *80:* 757, 1950.

FANCONI u. BICKEL. Die chronische Aminoacidurie bei der Glykogenose u. Cystinkrankheit. Helv. Paediat. Acta, Vol. *4:* 359, 1949.

FANCONI u. CHASTONAY: Die D-Hypervitaminose im Säuglingsalter. Livre jubilaire édité à l'occasion de l'anniversaire de la Fondation de la maison Hématogène HOMMEL, Zürich, 1950.

FRANK: Über die wichtigsten Krankheitsbilder, die durch Störung der Rückresorption in der Niere entstehen, usw. Med. Welt, *20:* 403, 1951.

HOTTINGER: Über Cystindiathese. Ann. Paediatr. *156:* 257, 1941.

KOSENOW: Symmetrische Umbauzonen bei Säuglingsrachitis, Milkman-Syndrom? Z. Kinderheilk. *69:* 191, 1951.

LIGNAC: Über Störung des Cystinstoffwechsels bei Kindern. Münch. med. Wschr. *71:* 1016, 1924,.

LINNEWEH: Kongressberichte der 50. Tagung der Dtsch. Ges. f. Kinderheilk. Lübeck 1950. — Klin. Wschr. (im Druck).

MILKMAN: zit. EWERBECK.

STOWERS u. DENT: zit. FANCONI (2).

STOWERS, DENT u. CAMERON: zit. FANCONI (2).

ULLRICH: Zur Klinik und Erbbiologie der Cystindiathese als übergeordnete Störung bei renalem Zwergwuchs und renaler Rachitis. Z. Kinderheilk. *66:* 154, 1948.

VAN CREVELD u. GRUNBAUM: Renal rickets and cystinuria. Acta Paediat. *29:* 183, 1942.

WALLGREN: Resistente Rachitis. Arch. Kinderheilk. *141:* 197, 1951.

WEYERS: Über die Wirkungen eines schwefelhaltigen Öls. Hamburg, 1947.

WUHRMANN u. WUNDERLY: Die Bluteiweisskörper des Menschen, Benno Schwabe, Basel, 1947.

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FROM THE QUEEN LOUISE HOSPITAL FOR CHILDREN, COPENHAGEN.
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Another Case of Niemann-Pick's Disease Observed in Denmark

by

AAGE VIDEBÆK

Niemann-Pick's lipoidosis is really a rare disease. Less than 100 cases have been reported in the world's literature, and there is no reason to believe that the disease has been frequently overlooked, as it begins in infancy and an enormous enlargement of the spleen and liver is an early and outstanding sign. The differential diagnosis from other causes of spleno-hepatomegaly may be quite difficult by the clinical signs alone, although moderate enlargement of the lymph nodes and brownish pigmentation of the skin on the extensor surfaces of the joints ought to arouse a suspicion. In more advanced stages the ophthalmological appearance (4) is so characteristic in about 60 per cent of all cases that ophthalmoscopy is decisive, since a cherry red macular area surrounded by a grey zone does not seem to occur in other conditions. At an earlier stage, however, rather characteristic "foam" cells are demonstrable in the blood and even more often in smears from the bone marrow, spleen, or liver. If Niemann-Pick's disease has occurred among siblings, the diagnosis is of course easier.

Niemann-Pick's disease was observed for the first time in Denmark in 1947 (7). The patient was a boy in whom the condition was diagnosed at the age of 2 years and who lived until he was $5^1/_2$ year old. Later, a brother of his exhibited symptoms of Niemann-Pick's disease. His case history is as follows:

The boy is the youngest of a family of 5. The eldest sister is 10 years of age and healthy, another sister died at 3 months from pneumonia, a

brother died from Niemann-Pick's disease at 5 1/2 years, and a sister aged 4 years is healthy. The parents are in good health. There are no Jews in the family. The patient was born at term in the home after a normal labour of 4 hours. He was breast-fed and received an addition of vitamins until the age of 4 1/2 months and developed normally. When he was 5 months of age, however, his mother discovered that both spleen and liver were enlarged, and the baby was admitted to the Queen Louise Hospital for Children on Oct. 28, 1950.

Examination on admission: Length 70 cm (67 cm being normal for the age), weight 7.5 kg (7.5 kg being normal for the age and 8.4 for his length). He looked healthy. There was no jaundice; a trace of diffuse pigmentation was observed on the dorsal aspect of the fingers. Vision appeared normal. Ophthalmoscopy showed normal macular areas and optic discs. Hearing seemed unaffected. Small lymph nodes were palpable in all regions. Auscultation of heart and lungs was normal.

The abdomen was somewhat large. The liver reached to the iliac crest, its surface was smooth and indolent. The spleen was palpable 3—4 cm below the costal border. Circumference of the abdomen 42 cm. The swelling of the spleen and liver increased somewhat during the stay in the department.

No abnormal neurological findings. No oedemas.

The urine did not contain albumin, sugar, or blood. Moro and Mantoux tests were negative. Microscopical examination of the urine failed to reveal any abnormal elements. The stools did not contain pathogenic bacteria. S.R. 6 mm, 15.3 g Hb. per 100 ml, colour index 0.7 reticulocytes 0.6 per cent, leukocytes 13,000—14,000. Differential count normal. The bone marrow smear showed normal distribution of the cells, but several "foam" cells with the same appearance as had been observed in his brother who had died with Niemann-Pick's disease. "Foam" cells could not be demonstrated in the sputum.

Clotting time 4—6 min. Prothrombin time normal. Fragility test: haemolysis began at 0.48 per cent and was complete at 0.32 per cent. The number of eosinophils ranged from 200 to 500 per cubic mm, a decline occurred during the Thorn test. Thrombocytes 480,000.

Fasting blood sugar 95 mg per cent. Glucose tolerance curve was very low and short.

X-ray examination of the skeletal system failed to reveal abnormalities. There was no calcification in the region of the adrenals; an X-ray of the chest showed a mottled pattern diffusely in both lung fields.

No excretion of fat in the urine. Excretion of 17-ketosteroids about 1.0 mg in the 24 hours (normal). Fractional determination of the serum lipoids showed: total fat 1335 mg, phospholipoids 363 mg, total cholesterol 284 mg, free cholesterol 117 mg, and neutral fat 708 mg per 100 cc.

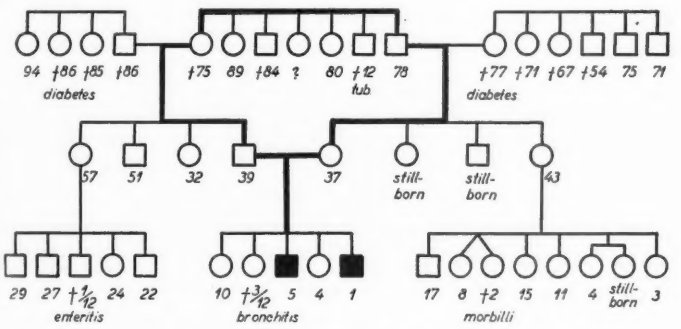

Fig. 1. Pedigree chart for two brothers with Niemann-Pick disease.

During the stay in hospital the temperature remained practically normal and the weight was constant.

After the examinations were finished, the baby was discharged at the parents' request.

Discussion

In 1949 the writer reviewed the literature on Niemann-Pick's disease up to 1948 and reported a typical case of the disease occurring in a Danish boy (7). The occurrence, the clinical and pathological features of the disease, its course and prognosis were discussed on the basis of 73 cases. The significance of heredity is borne out by the occurrence of the disease among siblings in at least 9 cases (for references cf. 7), by the common co-existence of developmental anomalies, by the fact that consanguinity has been reported in a few cases (2, 5, 6), and that the victims have been Jews in 30 out of 53 cases (7). However, detailed information about the family is given in only a few cases.

In the report of the first Dansih case it was stated that no case of consanguinity had occurred in the family. As apparent from the figure, however, this has proved to be wrong, since the parents of the two children are first cousins. Niemann-Pick's disease does not seem to have occurred in the same or other generations of this family. Regrettably, it proved impossible to study other members of the family, as would have been indicated, particularly after the demonstration in a Swiss family of several

cases of hypercholesterolaemia or spleno-hepatomegaly among the adult relations of a patient suffering from Niemann-Pick's disease (3). In the present case the concentration of the phospholipoids of the serum was increased as were the total cholesterol and the amount of neutral fat. Increased serum lipoid values were found also in the patient's brother who had Niemann-Pick's disease (7), and more or less marked lipaemia has been reported by a few other workers (1, 2, 6). Two distant relatives of the present patient suffered from diabetes mellitus, but, of course, it is far from certain that any relationship exists between these two conditions.

Summary

A case of Niemann-Pick's disease is reported in a boy of 5 months. He exhibited increased values of phospholipoids, cholesterol, and neutral fat in the serum. The same condition was previously reported in his elder brother, but does not appear to have occurred among more distant relatives. The parents are first cousins.

Un autre cas de maladie de Niemann-Pick observé au Danemark.

On rapporte un cas de maladie de Niemann-Pick chez un garcon de 5 mois. Il présentait des valeurs augmentées des phospholipides, du cholesterol et des graisses neutres dans le sérum. Le même syndrome a été antérieurement rapporté chez son frère ainé, mais ne semble pas être survenu chez des parents plus éloignés. Les parents sont cousins germains.

Eine weitere Beobachtung von Niemann-Pickscher Krankheit in Dänemark.

Ein Fall von Niemann-Pick-Krankheit bei einem 5 Monate alten Knaben wird beschrieben. Er zeigte erhöhte Werte von Phosphorlipoiden, Cholesterol und Neutralfetten im Serum. Die gleichen Gegebenheiten waren früher bei seinem älteren Brüder berichtet worden. Die Eltern sind nicht weitläufige Verwandte, sondern Cousins.

Nuevo caso de enfermedad de Niemann-Pick observade en Dinamarca.

Se describe un caso de enfermedad de Niemann-Pick en un niño de 5 meses. Mostraba valores elevados en el suero de fosfolípidos colesterol

y grasa neutra. La misma enfermedad había sido descrita previamente en un hermano anterior y no había aparecido entre otros mas distantes. Los padres son primos hermanos.

References

1. Freudenberg, E.: Klinische Beobachtungen und Untersuchungen an einem Zwillingspaar mit Niemann-Pickscher Krankheit. Zschr. Kinderh. *59:* 313, 1938.
2. Karelitz, S.: Personal communication cited by Rothstein, J. L. & Welt, S.: Infantile amaurotic family idiocy. Am. J. Dis. Child. *62:* 801, 1941.
3. Pfändler, U.: La maladie de Niemann-Pick dans le cadre des lipoidoses, Schweiz. med. Wschr. *76:* 1128, 1946.
4. Rintelen, F.: Die Histopathologie der Augenhintergrundsveränderungen bei Niemann-Pickscher Lipoidose, Arch. Augenh. *109:* 332, 1936.
5. Sobotka, H., Epstein, E. Z., & Lichtenstein, L.: The distribution of lipoid in a case of Niemann-Pick's disease associated with amaurotic family idiocy. Arch. Path. *10:* 677, 1930.
6. Tow, A. & Wechsler, H. F.: Lipoid histiocytosis: Case report, N. York State J. M. *33:* 203, 1933.
7. Videbæk, A.: Niemann-Pick's disease. Acute and chronic type? Acta pædiat. *37:* 95, 1949.

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FROM THE CHILDREN'S HOSPITAL, ODENSE, CHIEF PHYSICIAN: J. FLAMAND CHRISTENSEN, AND ODENSE MEDICAL SCHOOL BOARD, CHIEF PHYSICIAN: HJ. HEERUP.

Psychogenic Anorexia and Hyperorexia among Siblings

by

KAI TOLSTRUP

It is a well-established clinical observation that certain kinds of anorexia have psychogenic causes. Through HILDE BRUCH's works on infantile obesity we have now become acquainted with a psychogenic disturbance of the appetite to the opposite effect: the pathologically increased appetite, or hyperorexia.

It seems likely that the two contrary disturbances of appetite should have aetiological factors in common and this thought has found expression in the literature on anorexia nervosa. Thus, several authors have described anorexia nervosa as being preceded by obesity (SHELDON, LUTZ, RAHMANN & al.). Instances of the opposite phenomenon have been seen: a poor appetite followed by a psychogenic hyperorexia. Apparently in these cases it is a matter of a labile regulation of the appetite in the child in question, where the specific situation may involve either abnormal increase or abnormal decrease of appetite.

In an inquiry primarily aimed at testing HILDE BRUCH's theory on psychogenic obesity[1] cases have occasionally been observed of anorexia in siblings of adipose children. As it was reasonable to conclude that these adipose children developed their increased appetites owing to unsatisfactory social surroundings, it was natural to investigate their brothers and sisters with anorexia. Below is the story of two sisters, one with anorexia and the other with hyperorexia, and two brothers with the same characteristics,

[1] To be published together with IVERSEN, JUEL-NIELSEN, QUAADE and ØSTERGÅRD.

in both cases accompanied by a description of their disturbances of appetite. By comparing anorexia with hyperorexia in the same surroundings — i. e. the same home — the psychogenesis is illustrated more strongly than would be possible if these symptoms were only found singly.

Family I

Anorexia

I. G. is the second of two, a girl aged 2, sent to the Odense Children's Hospital on account of persistant anorexia. The mother explains that "there has been much nonsense about her ever since her birth" — indeed, even during the latter part of pregnancy. Birth is said to have lasted three weeks. At this time the mother's nerves were highly strung. Though she does not say in so many words that she had not wanted the child, she at least suggests that it was not expressly desired. I. has always been quarrelsome, early reacting violently if interfered with, this being particularly manifest at meals, which used to be a struggle. Her refusal to eat is said to have started at the time of her weaning, i. e. when she was eight days old. It has increased ever since, gradually adding complications of obstipation and vomiting. At first the vomiting came as a culmination at the end of the eating-struggle, later, however, also in the evening just after she had fallen asleep. As an illustration of the degree of anorexia the mother states that in the period immediately preceding hospitalization the child has lived solely on cod-liver oil and hip juice. Convinced of the importance of vitamins the mother has been careful to force down at least these. I. is described as an altogether very restless and vociferous child, and finally the mother has to give up and the child is sent to hospital.

On her admission she is described as a tall, frail-looking, thin child. Weight: 12.3 kg (w. at birth: 3.5 kg). Height: 93 cm. Haemoglobin (Sicca): 90 per cent. Moro: Negative. Blood sedimentation rate: 4 mm/1 hour. Microscopic inspection of urine showed no abnormal constituents. Ventriculogram: nothing abnormal. At the objective examination nothing noteworthy was found except a small prolapsus recti.

During her five weeks' stay at the Children's Hospital her psychical conduct proved perfectly natural. At first she ate sparingly, and during one of the first nights she vomited once after having gone to sleep. Gradually, subject to regular nutrition, she became a better eater. Obstipation disappeared after a light laxative treatment. When dismissed her purgation was spontaneous and of normal density.

She put on 1.6 kg in hospital. Afterwards she was not too bad at eating at home. Vomiting and obstipation disappeared. When she was

seen again 18 months after leaving hospital, the mother had no other complaint than that she was still irascible, obstinate, self-asserting. However, she was still slight and a small eater, but evidently the mother has reconciled herself to this state of affairs.

Hyperorexia

Her three-year-older sister, H., six years of age, was sent to the Children's Hospital one year later on account of adiposity. In contradistinction to the sister she has presented no kind of eating-symptoms in her early years. She was suckled for five months and developed normally until she was about three years old. Then — simultaneously with the birth of her sister — she began putting on weight, and since then she has grown steadily fatter. As she has recently got so fat on the inner side of her thighs that she virtually "grinds" her trousers asunder, the parents think that this is quite enough.

Her food anamnesis at once reveals that this is a case of genuine hyperorexia. She always has an appetite, she can eat at any and every hour. As moreover she gets fat-forming food (e. g. hot milk and honey every morning) and the parents give her many sweets, the reason of her fatness is obvious. Her bodily activity is lively. She bites her nails and sucks her fingers. Apart from this she presents no special symptoms. She is an easy child at home and gets on well with her playmates. It does not upset her that her school-fellows call her "Fatty"; on the contrary, she is a little proud of it.

On admission she is described as tall, well-grown, very obese, with fairly diffuse spread of subcutaneous adipose tissue. Height: 134 cm. Weight: 42.2 kg (w. at birth 3.5 kg). X-rayed cranium and sella turcica: nothing abnormal. Haemoglobin (Sicca): 95 per cent. Inspection of urine: no abnormal constituents. Psyche: Very confident and talkative, somewhat inclined to posing, conceited, precocious. Intelligence undoubtedly high. She gets along well with other children.

On normal hospital diet in moderate portions she lost weight reasonably. Later, however, a well-defined moderate diet sheet (1 325 calories) proved necessary. It did not seem to give her any trouble to keep to the diet. To some extent she made up for it by gum-chewing and — when she believed herself unobservered — thumb sucking. She lost 3.9 kg in less than six weeks. When checked about two months after being sent home her weight was stationary. This is accepted as satisfactory, seeing that she has grown several centimeters during this time.

Surroundings

Outward conditions are excellent. The father is a great landowner. There is plenty of room, apparently plenty of money, and abundance of food. Food plays a great part in family life. The mother loves food

and must always be careful what she eats in order not to get fat. Naturally the children's behaviour shows manifest symptoms in their relation to food.

The parents are not very outspoken, but nevertheless it appears that their married life is not harmonious. They disagree on the education of the children and accuse each other of spoiling them. But it seems to be a personal discord between the parents mutually — rather than just a difference of opinion on general educational principles — that characterize their attitude to the children. At least it is obvious that the children's attitude to their parents is not of a normal cordial nature.

The clue to the understanding of the children's eating-symptoms will be found in the elder girl's hyperorexia, which began at the birth of her sister. The two sisters have always been on bad terms. The elder, H., — when first examined in hospital — declared at once and on her own accord, "My little sister is a naughty girl. She scratches, she tells lies, and she steals," thus taking up the flattering position of a good little girl at home, standing out in relief against the background of baby's naughtiness. Her very hyperorexia is an indication of good manners. By eating much she has maintained her position in her mother's good graces, which she thought threatened when baby was born. No means could be more appropriate than eating, every day H. was a witness of mother's struggle to make baby eat. And in these emotionally unstable surroundings it may have been necessary for her to stick to her advantage in this way. Perhaps it has been more than a means to strengthen her position against her sister; perhaps it was an indication of emotional starvation: eating became a compensation for that feeling of safety which the mother failed to give her.

The primary stage, then, was the anorexia of little I. In its turn this eating-inhibition is probably resultant of a certain antagonism to the mother, dating from birth, or rather from before birth. I. was presumably not wanted — though the mother does not expressly admit it. All that the mother says about I. stresses the point that she is "difficult"; possible hostile feelings on the mother's side are conveniently disguised by emphasizing the child's naughtiness. It is reasonable to explain I.'s anorexia as a consequence of the mother's unconscious antipathy towards this child.

That H. has succeeded in gaining the upper hand over baby by eating is clearly evidenced by what the parents say about her as a peaceful and easy child in contradistinction to baby. Nor did her gluttony rouse their attention in anything like the same way as baby's eating-inhibition. For nothing seemed more natural to the parents than to eat much.

The following double case report on the eating-symptoms of two brothers does not display the same aetiological pattern, but still contributes to the understanding of the relations between anorexia and hyperorexia.

Family II

Hyperorexia

P. was 13 years old when first seen. (He was registered by the school doctor as weighing excessively.) He is the eldest of three brothers, the others being three and seven years younger.

He has grown progressively fatter through the last four years. In a food-diary which he was induced to keep for a week, he shamelessly reveals the reason: he eats frequently and much and at most irregular intervals, he is always hungry, and his food is unvaryingly carbohydrate. At the same time he moves no more than he can help.

He presents a rather chequered anamnesis morbi. From his third year he suffered from fits of asthma. These symptoms have gradually disappeared, but they have caused much concern, and on several occasions he has been sent to hospital, where no fits of asthma occurred and no organic disease was found. Moreover he has until recently suffered from enuresis nocturna. He still has to get up once every night to make water. A couple of years ago he suddenly showed signs of unsettled behaviour, he was 'unmanageable', he got the most puzzling ideas into his head such as stripping in mid-winter or putting on winter dress in summer. The parents went to the family doctor, who on the same occasion called their attention to his fatness and declared that there was cryptorchism. This made the parents even more concerned and more intent on looking after his doings.

At the objective examination a considerable adiposity was found with an even distribution of subcutaneous fat. Weight: 57.8 kg (w. at birth: 4 kg). Height 152 cm. The rest of the examination showed natural conditions, especially no cryptorchism or hypogenitalism. Psychically he was very sulky and unwilling to cooperate, but very *well-behaved.*

Anorexia

His youngest brother, J., was six years old when first seen. The mother complained that she could not manage to tell P. to eat more and J. to eat less. Since J. was a baby he has been a poor eater. Already at six months of age he was admitted to the Children's Hospital, Odense, owing to anorexia and vomiting. The department's diagnosis was dystrophia. No explanation of his symptoms was found during his stay. He ate but little and only put on 100 g in four weeks. During the following years he constantly suffered from periodic vomiting — always in connection with meals — and continued anorexia. He has repeatedly been examined by the family doctor and is under observation from the school doctor. No disorder has ever been found to explain the anorexia and he presented no other symptoms.

The mother described him as an easy and manageable child, perhaps a little 'girlish' (i. e. he prefers to play with girls).

The objective examination revealed a nice, but small, slender, thin child, who otherwise displayed no noteworthy traits. Wieght: 18.3 kg (w. at birth: 3.5 kg.). Height: 114 cm. Psyche: friendly and ingratiating, unlike his brother, but like him in being very *well-behaved.*

The school psychologist kindly examined him and reported as follows:

"A Binet-Simon intelligence test gave this result: Age 8.3, IQ 112. Normal diffusion from 7—11 years. Range of memory somewhat narrow. At first he seems to be rather reserved and shy, finger in mouth, later on he tends to unbend. He seems to be sensible and fairly intelligent, corresponding to IQ above. He works with concentration and interest.

The effect produced by a short talk as well as by the impression during the intelligence test is that he is somewhat babyish, not only as to bodily growth, but also as regards character and social development. He seems to be somewhat overprotected and dependent, e. g. he prefers to sleep in his parents' bedroom. No differences with his schoolfellows, who presumably also regard him as Baby, one they like and treat forbearingly. Most likely there is a reciprocity between bodily development and development of character, whatever the primary agent may be.

Pedagogic tests show good position in schoolwork. He is rather slow, but comprehending, at arithmetic. His form mistress corroborates this. In class he does his sums slowly, on the whole his reaction is slow and without originality. Like the other pupils he gets one sandwich for schoollunch, but he is always the last to finish it.

(sign.) M. Danielsen."

Surroundings

Father's job is permanent and fairly well paid; but the mother has to do some home work for a dressmaker's firm. The parents are hardworking with a tendency to imitating their betters. It is typical for the tenor of the home that the children are flawlessly well-behaved — when they are not at home, that is! It is the mother's pride that she has laid all educational stress on good manners and nice appearances. She has had to sacrifice harmony at home to perpetrate her plan, which price has not occurred to her. She is drilling and bickering all day long. The children must obey *on the spot;* they never do, the result being a perpetual state of irritation and slapping. It is important that the boys get on in the world, that they obtain safe jobs of some social standing. The mother is the chief force behind this exacting parental principle. The father seems to fade out beside her, he cannot check her aspirations, he does not want to, even. She complains of her own energy, she cannot help working, her hands must be occupied. However, on one or two occasions I

find her dozing and with hands peacefully at rest. She is always taking sedatives, so as to be able to cope with her work.

The two brothers mentioned here bear the stamp of their mother's perfectionist attitude to life. Whereas number three — born between the other two — evidently gets on comparatively unhurt, it is obvious that the eldest, P., reacts vehemently, while the youngest seems to acquiesce.

P.'s changing symptoms since his third year — (viz. fits of asthma; enuresis nocturna; the violent behaviour pertubation a couple of years ago; at last hyperorexia) — may be interpreted as a reaction to his mother's constant claims on him, and as implying emotional unstableness generally. He is more antagonistic against his mother than are the other two. He gets on her nerves, they are always engaged in a regular fight for power, in which P. tries a variety of weapons.

The youngest, J., has apparently submitted. He is a good boy, and an easy one who always gives way. His only weak point is his anorexia; it does not manifest itself, though, as violent fights during meals, but precisely as *weakness*. This weakness suggests itself, then, as *his* reaction against the mother. Most likely it originates from a dyspepsia in his babyhood, and since then it has proved useful in holding the mother, whereas P. has always had to change symptoms. Here anorexia may be taken as a consequence of regressive mechanism.

Discussion

First it should be emphasized that the above inquiry is not profound. The investigation of surroundings has been by way of asking questions generally. Naturally the opinions enounced below are of a corresponding limited value.

What is aetiologically interesting in these particular reports is the fact that the same family frame provokes anorexia in one child and hyperorexia in another. However, it must be stressed from the start that surroundings under a more comprehensive aspect — viz. the home as such — being common for two brothers or sisters need not necessarily imply that their positions are identical in the surroundings, if the term is taken in a more limited sense, namely the footing on which they find themselves with parents, brothers, sisters. In fact, there will always be a difference in details. In this connection it is an important point that exactly where the relations between brothers and sisters contribute decisively to the defect in home life, the children have for this very reason a different position. Still, brothers and sisters have so many

things in common in their surroundings that it is a reasonable question to ask why they react with diametrically opposed symptoms of behaviour. Is there a reaction-type disposed for hyperorexia, and another disposed for anorexia?

In her investigations on psychogenic adiposity HILDE BRUCH lays chief stress on the constellation of the family frame. She does not venture on any attempt to analyse whether there might be natural tendencies that induce a particular child to react on frame-defect with hyperorexia, but she suggests that the problem exists. And behind her descriptions of the typical fat child we are conscious of a characteristic of passivity. Her adipose type lacks the ability of protest, his patience is astounding. LEVY describes a psychical characteristic in 33 children with Frohlich's syndrome and finds that on the whole they are 'submissive' and fall in line passively. He seeks the explanation in endocrine disturbances, but does not prove any probable presence of endocrine trouble, nor is his criterion for Frohlich's syndrome — the distribution of the fat alone — convincing. His descriptions may as well involve children with simple adiposity and with a characteristic acquiescent mind, whose aetiology is undetected.

It is a well-known fact that anorexia often appears as a protest reaction against parent's compulsive insistence on eating. Furthermore several authors (ROSE, RUEGG) look upon anorexia as a universal reaction against comprehensive changes in habits of life, against every kind of development and growth. According to this conception anorexia should appear particularly in critical periods in the child's development, when being weaned, at the age of stubborn defiance, at beginning of school-age, etc. This is most explicit in anorexia nervosa when this ailment manifests itself in late puberty and young women. Thus a more *active* reaction-type is suggested in persons with anorexia in contradistinction to the characteristic passive psyche in children with hyperorexia, quoting the authors mentioned above.

Against a dispositional reaction-type for either anorexia or hyperorexia is the phenomenon mentioned in the introduction that both kinds of reaction can be found in the same person at different times.

The deeper symbolism that the psycho-analysts attach to the symptoms of anorexia and hyperorexia will not be discussed. Not because these theories are underrated but because this article, as already said, lies on another level without attempts at deep diagnostics.

What conclusion can be drawn from the case reports on siblings, reproduced in this article, as to the problems which have been considered? Is there a psychical peculiarity — perhaps constitutional — coupled with the symptoms of anorexia and hyperorexia?

In both families the two siblings are depicted as contrasts: one is easy and manageable, the other is intolerable, difficult. One seems passive, submissive, the other actively protesting, aggressive. The same types suggest themselves as those that should characterize hyperorexia and anorexia respectively. Only there is the decisive contrast that while the semblance is perfect in Family I, the tables are turned in Family II, where anorexia is connected with the passive type, and — per contra — hyperorexia combined with aggression. Thus, these cases do not seem to indicate any congruity between a precise symptom and a corresponding attitude, active or passive.

Further it must be emphasized that hyperorexia in the girl in Family I was born, as it were, of the situation — bred as a countercheck to the sister's anorexia, as a negation of her eating-inhibition. This is a case against the theory that increased eating should be a predisposed reaction against a psychical stress. Quite obviously it is a reaction against *surroundings*. It is more difficult to decide what is influence from surroundings and what is constitutional disposition when considering the irregularities of appetite in the three other children. J. in Family II has probably developed his anorexia already as a baby through the aetiologically vague ailment for which he was sent to hospital, and since then this symptom has been his refuge when the psychical pressure at home got too heavy. The hyperorexia of P., his elder brother, does not willingly submit itself to an equally simple explanation. There is nothing to indicate that it should be regarded as a reaction against his brother's anorexia.

Why is it that the constellation hyperorexia-anorexia appears

precisely in these families? As to Family I it is natural, seeing that food plays a great part in this house. A corresponding gastronomic enthusiasm does not exist in family II, nor can any spontaneous explanation be found why this perfectionist home should cause *appetitive* disturbances.

No general aetiological conclusions can be drawn from these cases of hyperorexia-anorexia. They are too few, and the diagnostics are not sufficiently profound. It is necessary to make further and more comprehensive studies on the psychogenesis concerning these symptoms — both as to circumstances in the surroundings and as to constitutional background. Up till now they have been dealt with separately. It is the object of the present article to point out that it might be advantageous to consider them together. It is suggsted that the term *psychogenic dysorexia* be introduced as a joint designation for the two appetitive disturbances. At the same time there is much to be said for the term *hyperorexia*, which should be used as much as possible in clinical language in association with the diagnosis of adiposity. Already the word *anorexia* is closely associated with being lean, which makes the aetiology. The desirability of having a similar suggestive term for being fat is obvious.

Summary

An examination of two sisters with psychogenic hyperorexia and anorexia respectively; and two brothers of another family with the same symptoms, make up the background of a discussion of the relations between anorexia and hyperorexia.

In Family I anorexia in the younger girl seems to be the primary disturbance of appetite in the surroundings. The sister's hyperorexia should be regarded as a direct outcome of the younger sister's eating-inhibition, an attempt to keep up the position at home that she felt threatened when the little one was born. The adequacy of this mechanism appears from the predominant part that food plays in the house.

In Family II there is no such connection between the symptoms of the two brothers. The younger suffers from anorexia, in this case a regressive mechanism, probably with a dyspepsia in babyhood as starting-point. His brother has during his early years displayed various psychogenic symptoms — fits suggesting asthma, enuresis nocturna, several behaviour-disturbances — and finally hyperorexia, which apparently is a link in the chain of symptoms. The family is dominated by a perfectionist

mother. The reason why both children should react against these surroundings with disturbances of appetite does not appear from the examination.

Two different kinds of psychical expression are found in these four children, partly a passive, non-protesting type, partly an active, aggressive type. In one family the passive expression is combined with hyperorexia and the active one with anorexia; in the other family it is the other way round.

The advantage of connecting anorexia with hyperorexia is emphasized. The introduction of the common term *psychogenic dysorexia* is suggested for the symptoms concerned, in order to call attention to the common source: disturbed appetite.

Anorexie et hyperorexie psychogènes chez des frères et sœurs.

L'examen de deux sœurs, avec respectivement anorexie et hyperorexie psychogènes, et de deux frères d'une autre famille avec les mêmes symptomes, constitue le fond d'une discussion, concernant les relations entre anorexie et hyperorexie. Dans la famille I, l'anorexie chez la plus jeune semble être le premier trouble de l'appétit, dans l'entourage. L'hyperorexie de la sœur serait considérée comme une conséquence directe de l'inhibition de sa plus jeune sœur pour la nourriture, un essai de conserver sa position à la maison, qu'elle a senti menacée, quand sa petite sœur est née. La part prédominante que la nourriture joue dans cette maison semble justifier ce mécanisme. — Dans la famille II, il n'y a pas de rapport entre les symptomes des deux frères. Le plus jeune souffre d'anorexie: dans ce cas, c'est un mécanisme régressif, probablement avec une dyspepsie dans l'enfance, qui est le point de départ. Son frère a, durant ses premières années, présenté divers symptomes psychogènes — accès d'asthme psychopathiques, énurésie nocturne, troubles sévères du comportement — et finalement hyperorexie, qui, apparemment, n'est qu'un anneau de cette chaîne de symptomes. La famille est dirigée par une mère perfectioniste. L'examen ne décèle pas le motif, pour lequel ces deux enfants réagiraient contre leur entourage, par des troubles de l'appétit. Deux modes de manifestation psychique sont trouvés chez ces quatre enfants: l'un passif, de type sans protestation, l'autre actif, de type agressif. Dans une famille, l'expression passive est combinée avec l'hyperorexie, et l'active avec l'anorexie; dans l'autre famille, c'est l'inverse. On insiste sur l'avantage des relations entre anorexie et hyperorexie. L'introduction du terme commun, *dysorexie psychogène*, est suggérée, pour les symptomes qui les concernent, afin d'attirer l'attention sur leur source commune: un trouble de l'appétit.

Psychogene Anorexie und Hyperorexie bei Geschwistern.

Eine Untersuchung von 2 Schwestern mit psychogener Anorexie bzw. Hyperorexie und von 2 Brüdern einer anderen Familie mit den gleichen Symptomen bilden den Hintergrund einer Diskussion über die Beziehungen zwischen Anorexie und Hyperorexie. In der Familie I schien die Ursache der Anorexie bei dem jüngeren Mädchen im Milieu zu liegen. Die Hyperorexie der Schwester könnte als eine direkte Folge der Nahrungsverweigerung der jüngeren Schwester aufgefasst werden, als ein Versuch die Position zu Hause wiederzuerlangen, die sie verloren glaubte, als die Jüngere geboren wurde. Adäquat erscheint dieser Mechanismus bei Berücksichtigung der überragenden Rolle, welche das Essen in der Familie spielt. — In der Familie II ist keine solche Verbindung zwischen den Symptomen beider Brüder. Der Jüngere leidet unter Anorexie, hier ein regressiver Mechanismus, wahrscheinlich von einer Dyspepsie in der früheren Kindheit herrührend. Sein Bruder hat schon frühzeitig verschiedene psychogene Symptome — Asthma vortäuschende Anfälle, Enuresis nocturna, Störungen im Benehmen — und schliesslich Hyperorexie entwickelt, die augenscheinlich nur ein Glied in der Kette der Symptome ist. Die Familie wird von einer perfektionistischen Mutter betreut, ein Grund einer Milieureaktion konnte bei der Untersuchung nicht gefunden werden. Zwei verschiedene Typen psychischer Ausdrucksformen wurden bei diesen 4 Kindern beobachtet, ein passiver, nicht protestierender Typ und ein aktiver, aggressiver Typ. In einer Familie ist die passive Ausdrucksform verbunden mit Hyperorexie und die aktive mit Anorexie; in der anderen Familie liegen die Verhältnisse umgekehrt. Der Vorteil, eine Verbindung zwischen Anorexie und Hyperorexie zu ziehen, wird betont. Die Einführung des Ausdruckes "psychogene Dysorexie" wird vorgeschlagen, da die gemeinsame Ursache, die Appetitstörung damit berücksichtigt ist.

Anorexia psicogénica e hiperorexia en niños hermanos.

El exámen de dos hermanas con hiperorexia y anorexia psicogénica respectivamente y de dos hermanos de otra familia con los mismos síntomas dá fondo a la discusión de las relaciones entre anorexia e hiperorexia. En la familia primera la anorexia en la mas joven de las niñas mostraba ser la alteración primaria del apetito en el medio. La hiperorexia de la hermana debía ser considerada como la causa directa de la inhibición en el comer de su hermana atendiendo con ello a recuperar la posición familiar que ocupaba antes de nacer la otra niña. La frecuencia de este mecanismo suele ser predominante. En la familia segunda no se halla una conexión entre los síntomas de los dos hermanos. El mas joven tiene anorexia en este caso probablemente como mecanismo regresivo de una dispepsia de la primera edad como punto de partida. Su hermano tuvo durante los primeros años trastornos con síntomas psicogénicos

— accesos que sugerian asma, enuresis nocturna, varios trastornos de la conducta —, y finalmente hiperorexia la cual entra también en esta cadena de síntomas. La familia era dominada por una madre perfeccionista. La razón por la cual ambos niños reaccionaban frente a este medio ambiente con trastornos del apetito no aparece claramente en el exámen. Dos diferentes clases de expresión física se hallan en estos cuatro niños, una pasiva de no protesta y otra activa de tipo agresivo. En una familia la expresión pasiva va combinada con hiperorexia y la activa con anorexia: en la otra familia ocurre en sentido inverso. Se resalta la ventaja de relacionar la anorexia con la hiperorexia y se sugiere la introducción del término común *disorexia psicogénica* en órden a llamar la atención sobre los síntomas que tienen una fuente común: el apetito alterado.

Literature

Bruch, Hilde: The Family Frame of Obese Children. Psychosom. Med. *2:* 141, 1940.

Levy, D. M.: Aggressive-submissive Behaviour and the Froehlich Syndrome. Arch. Neur. Psychiat. *36:* 991, 1936.

Lutz, Jacob: Die Frage der psychischen Faktoren bei der weiblichen Spätpubertät. Zschr. Kinderpsych. *17:* 51, 1950.

Rahmann & al: Anorexia Nervosa with Psychiatric Observations. Psychosom. Med. *1:* 335, 1939.

Rose, I. A.: Eating-Inhibitions of Children. Psychosom. Med. *5:* 117, 1943.

Ruegg, Martha, quoted after Lutz.

Sheldon: Anorexia Nervosa with Special Reference to the Physical Constitution. Lancet, pag. 369, Febr., 1937.

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CASE REPORTS

Juvenile Xanthoma

by

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The skin changes spoken of as xanthoma have recently attracted much interest. This is because it has been realized that the changes should not be regarded simply as local lesions of the skin alone but as manifestations of a systemic disease.

Table 1 summarizes the various types of xanthoma and the usually co-existent systemic lesions as well as the levels of the serum cholesterol.

Table 1

Xanthomatosis (Cholesterolosis)

	Skin xanthoma	Systemic lesions
Primary essential xanthomatosis of the hypercholesteremic type	Xanthoma tuberosum Xanthoma planum	Xanthoma of the tendon sheaths the bile ducts the endocardium the blood vessels
Secondary xanthomatosis due to hyperlipemia and cholesterolemia	Xanthoma eruptivum	
Primary essential xanthomatosis of the normocholesteremic type	Xanthoma disseminatum	Xanthoma of the osseous system the dura the brain the lungs
	(Mb. Hand-Schüller-Christian)	
	Xanthoma juvenile (nevo-xantho-endo-thelioma)	None

Xanthoma tuberosum is commonest in adults. The manifestations consist of pea- to egg-sized yellow or yellowish-brown, soft tumours, that show a predilection for the extensor aspects of the elbows and knees.

Xanthoma planum. — Here the lesions are plaques of similar appearance to those seen in xanthoma tuberosum, commonly situated in the palms of the hands and in the eyelids.

In both of these types the blood cholesterol is generally increased and various internal organs such as the tendons, the bile ducts, the endocardium and the blood vessels are usually also involved by the xanthomatous lesions. The Norwegian MÜLLER was the first to correlate the various signs and symptoms of this disease.

Xanthoma eruptivum. — In this condition the clinical signs consist of small yellowish-brown papules surrounded by a halo of inflammation. They appear and disappear periodically according to the level of the serum lipoid. They occur in various diseases associated with increased serum lipoid, e. g., diabetes mellitus, nephrosis or essential hyperlipemia.

Xanthoma disseminatum is the commonest type of xanthoma in children. The skin changes usually consist of clustered pinhead-sized, yellow or yellowish-brown nodules. They are most frequently seen on the scalp, on the neck and in the antecubital fossa and may at first sight be mistaken for seborrhoeic eczema. Sooner or later changes appear in the skeleton, dura, brain and lungs, when the clinical picture is that of Hand-Schüller-Christian syndrome. The concentration of total fat in the blood and the serum cholesterol are both within a normal range.

Xanthoma juvenile is a rare variant. It was first described by ADAMSON (1905), who termed it congenital xanthoma multiplex. The next to report the condition was MCDONAUGH, who presented 1 case in 1909 and 5 in 1912. In view of his interpretation of the histologic appearance of the tumours he called them nevo-xantho-endotheliomas. This designation has been claimed inadequate by later investigators on the grounds that naevus cells have never been demonstrated (TANNHAUSER, LAMB & LAIN, SENEAR & CARO). A few cases have also been reported by WISE, JACOBI & GRUND, SENEAR & CARO, TANNHAUSER and by FREUD.

In juvenile xanthoma small wart-like papular lesions ranging in size from that of a pinhead to that of an almond are seen. The tumours are always solitary and show no tendency to cluster.

The lesion begins with a proliferation of reticulo-endothelial-elements. Lipoids are gradually deposited and some of the reticulum cells develop into foam cells and giant cells (Touton cells). Finally fibrosis progresses at an ever increasing rate.

Juvenile xanthoma is believed to be benign and to heal spontaneously by scar formation and, in contrast to xanthoma disseminatum, the internal organs are spared. But 3 cases are on record in which the mani-

festations were originally those of juvenile xanthoma but in which changes in the internal organs also appeared later.

LAMB & LAIN (1937) described a girl, who had juvenile xanthoma at the age of 3 months. At 14 months changes suggestive of metastases were seen in the lungs. At 16 months the skin changes and the pulmonary changes began to regress. At 5 years the lesions were still persistent but the child had developed normally.

In 1949, THELANDER & CRANE reported another case. It was a child who at the age of 3 months had xanthomatous nodules on the scalp. At 16 months hepatosplenomegaly was discovered. The white cell count was 45 700 but the differential count was normal. The child died at 26 months, when it had generalized lymphatic swelling, anaemia and leukopenia. Roentgenograms of the skull showed areas of bone rarefaction.

FREUD (1951) described a 2-year-old boy with juvenile xanthoma. Later the child had pulmonary and skeletal changes and the blood picture suggested leukaemia. During the following year he gradually lost strength and body weight.

As only some 10 cases of juvenile xanthoma are on record a case of the disorder seen recently at the Paediatric Clinic of the University Hospital of Lund is reported below.

Case Report

K. N., girl, born 22.6.1950 (Jr. 946/51).

The parents and her elder brother were healthy. None of the relatives known to have had metabolic diseases, nor had any of them had skin changes. Delivery was uneventful. Birth weight: 3,850 g. The child was breast fed for 6 months and then received ordinary diet. Development, both mental and physical was normal.

Soon after birth the mother had noticed a few yellowish-white raised lesions about 1 cm in diameter on the head of the child. These lesions gradually increased in number and appeared on one of the ears, on the neck, on the back and on the right arm.

On admission. — When first seen at the Department on 30.8. 51 the girl, who was of normal size for her age, was in a good general condition. Physical examination of the internal organs revealed nothing remarkable. A number of yellowish-white soft raised solitary tumours ranging from 0.5 cm to 2 cm in diameter were seen on the scalp, on the left side of the neck, on the back, on the right ear, on the right arm and on the right leg. The lesions were sharply defined and the surrounding skin appeared to be normal. (Fig. 1.)

Laboratory findings. — Blood: Hb. 72 per cent. Red cell count 3.66 million. White cell count 7,100. Diff. count: neutr. leukocytes 32 per cent, eosinophils 5 per cent, lymphocytes 60 per cent and monocytes

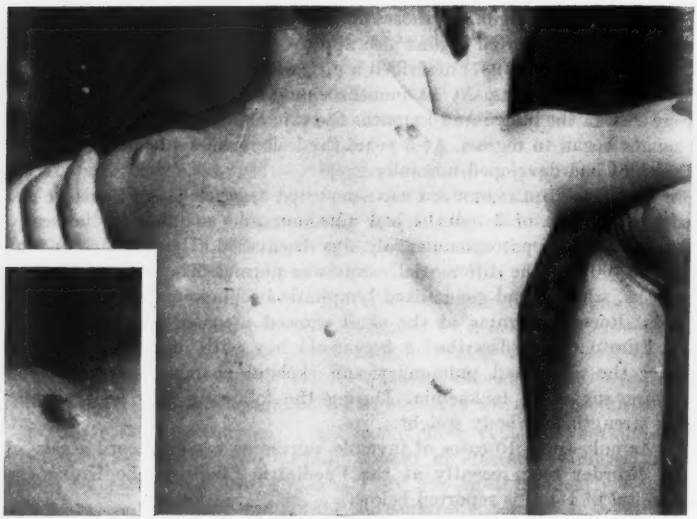

Fig. 1. Juvenile Xanthoma of a girl, aged 14 months. A close-up of one of the lesions is seen in the bottom left-hand corner.

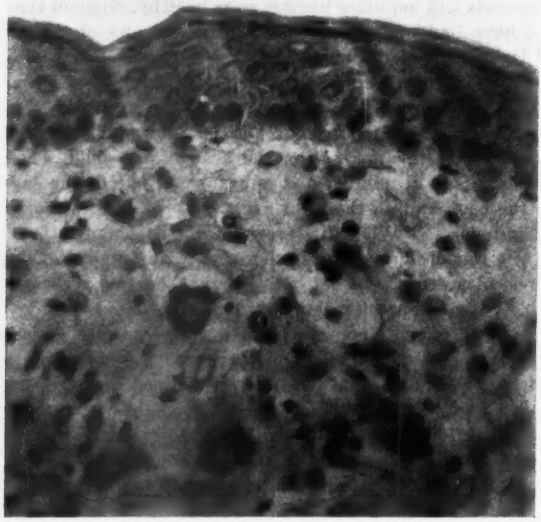

Fig. 2. Photomicrograph of a xanthomatous nodule of the skin showing several giant cells of the Touton type and foam cells.

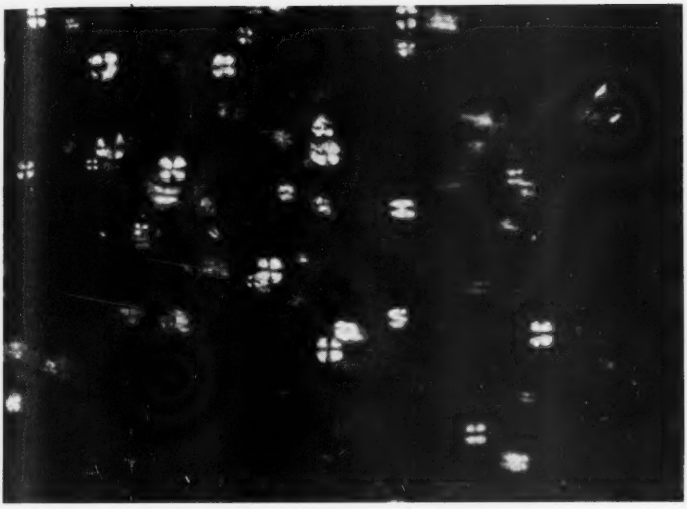

Fig. 3. When heated at 60° C for 15 minutes and inspected under polarized light, the lipoids appear as double-diffracting crosses. They therefore consist mainly of cholesterol compounds.

3 per cent. Tibial punctate showed no signs of a pathologic condition (Hellsten). Erythrocyte-sedimentation rate 4 mm per hour as determined by the miromethod of LANDAU. Cholesterol: 185 mg per 100 cc (free cholesterol 96 mg per 100 cc, sholesterol esters 89 mg per 100 cc). Total blood fat: 5 units using the method of Kunkel.

The daily amount of urine passed was normal. Heller and Almén negative. Sediment: normal.

Roentgenograms of the skull and of the chest were normal.

Mother's blood: total cholesterol 205 mg per 100 cc, free cholesterol 52 mg per 100 cc and cholesterol esters 153 mg per 100 cc. Total fat 4 units.

Father's blood: total cholesterol 100 mg per 100 cc. Free cholesterol 69 mg per 100 cc and cholesterol esters 31 mg per 100 cc. Total fat 6 units.

Histology. The skin covering a tumour removed for biopsy showed a thin atrophic layer of squamous epithelium. Underneath this in the corium were dense groups of large pale stained foam cells; a number of giant cells, usually with peripheral nuclei were also seen. A moderate deposition of round cells was seen in the immediate surroundings (Fig. 2.) Sections stained for fat showed foam cells rich in fat and some giant cells with fatty peripheral deposits. Examination of the sections under

polarized light revealed a large number of small needle shaped, strongly anisotropic crystals. On heating of the sections typical double-diffracting crosses of the type seen in cholesterol compounds were formed (Fig. 3). Diagnosis: Xanthoma. (N. O. BERG).

Discussion

A 14 month old girl had had practically since birth a number of wartlike, yellow, soft, solitary, pea- to bean sized tumours of the skin: they were spread diffusely over the scalp, over the trunk and over the extremities. The child had developed normally and had shown no other signs of disease. Biopsy showed the picture of xanthoma. As the blood cholesterol and the blood total fat were within normal ranges and as there was no reason to assume hereditary predisposition, it is probable that the lesions were manifestations of primary xanthomatosis of the normocholesteremic type. The question that naturally presents itself is whether the symptoms were precursors of Schüller-Christian's syndrome. Roentgenograms of the skull and of the chest were normal. Neither was there evidence of an involvement of the region of the hypophysis-hypothalamus. Neither did the clinical course fit in with Schüller-Christian's syndrome, because the latter is not so benign. Finally, the skin changes were not those usually seen in Schüller-Christian's syndrome with its xanthoma disseminatum.

The clinical course, the appearance of the xanthomatous nodules, which were solitary and showed no tendency to cluster, fit in better with the variant known as juvenile xanthoma. The prognosis of this disease is usually good.

Cases of typical juvenile xanthoma have, however, been described in which the internal organs also showed changes later (LAMB & LAIN, THELANDER & CRANE, FREUD). Therefore it is not possible to predict the prognosis in a given case, even though it is usually good. The child should be kept under observation in view of the possibility of later lesions of the internal organs.

Effective therapy is unavailable. To limit the dietary intake of fat and cholesterol is of no avail because the blood fat is not increased and because the metabolic disturbance is not systemic but localized to the tumour cells only.

Summary

A review of the clinical symptoms, particularly the skin lesions, of the various types of xanthomatosis is given. A case of juvenile xanthoma is then described. Characteristic of this type is that it usually appears within the first year of life and the skin lesions consist of small solitary tumours. The blood cholesterol and the total blood fat are within normal

limits. The internal organs are not usually involved and the prognosis is then good, but a few cases with later systemic lesions have been reported.

Xanthome juvénile.

Après une revue générale des symptomes cliniques, particulièrement des lésions cutanées, des différents types de xanthomatose, l'auteur décrit un cas de xanthome juvénile, une petite fille agée de 14 mois. La caractéristique de ce type de xanthome, c'est qu'il apparait habituellement dans le cours de la première année, et les lésions de la peau sont de petites tumeurs solitaires, de la taille d'une fève. Le cholestérol sanguin, et les lipides totaux du sang sont dans les limites des valeurs normales. Les organes internes ne sont habituellement pas lésés et le pronostic est bon, mais un petit nombre de cas avec des lésions tardives des organes internes ont été rapportés.

Juvenile Xanthome.

Nach einem allgemeinen Überblick über die klinischen Symptome, hauptsächlich die Hautläsionen der verschiedenen Typen von Xanthomatosis, beschreibt der Autor einen Fall von juvenilem Xanthom bei einem 14 Mon. altem Mädchen. Charakteristisch für diese Art ist das Auftreten im 1. Lebensjahr; die Hauterscheinungen bestehen in kleinen bis bohnengrossen, solitären Tumoren. Cholesterol und Gesamtfett im Blut liegen innerhalb normalen Grenzen. Die inneren Organe sind gewöhnlich nicht befallen und die Prognose ist dann gut; in einigen Fällen wurde jedoch über spätere Systemerkrankungen berichtet.

Xantoma juvenil.

Tras una revisión general de los síntomas clínicos y particularmente de las lesiones cutáneas de varios tipos de xantomatosis el autor describe un caso de xantoma juvenil. Es característico de este tipo el que usualmente aparece en el primer año de la vida y que las lesiones cutáneas consisten en pequeños tumores solitarios del tamaño de un guisante. El colesterol sanguíneo y la lipemia total muestran cifras normales. Los órganos internos generalmente no están afectados y el pronostico es entonces bueno, pero en algunos pocos casos se han descrito lesiones sistémicas tardías.

References

FREUD, P.: Evolution of Systemic Reticuloendotheliosis in Childhood. J. Pediat. *38:* 744, 1951.
JACOBI, R. & GRUND, J. L.: Endothelioma Cutis: Nevo-Xantho-Endothelioma. N. England J. M. *202:* 1247, 1930.
LAMB J. H. & LAIN, E. S.: Nevo-Xantho-Endothelioma. South. M. J. 1937, *30:* 585
McDONAUGH, J. E. R.: A Contribution at Our Knowledge of the Nevo-Xantho-Endothelioma. Brit. J. Derm. Syph. *24:* 85, 1912.
SENEAR, F. E. & CARO, M. R.: Nevoxantho-Endothelioma or Juvenile Xanthoma Arch. Derm. Syph. *34:* 195, 1936.
THANNHAUSER, S. J.: Lipidoses. Oxford University Press, 1950.
THELANDER, H. E. & CRANE, J. T.: Xanthomatosis J. Pediat. *34:* 490, 1949.
WISE, F.: Multiple Endothelioma of the Skin. Am. J. M. Sc. *157:* 236, 1919.

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Pseudohypoparathyroidism

by

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In 1880, the first anatomical description of the parathyroid glands was given by SANDSTRÖM (11), but it was not until 1925 that COLLIP (5) managed to prepare an active parathyroid extract that was able to raise the blood calcium level in parathyroprivic as well as normal animals.

At the beginning of this century cases were described with symptoms of hypofunction identical with those of post-operative hypoparathyroidism but with absence of the etiological factor, the operation. This disease was called idiopathic hypoparathyroidism and its chief symptoms are hypocalcemia, hyperphosphatemia, decreased urinary excretion of calcium and phosphorus but normal serum phosphatase, and due to the hypocalcemia symptoms of tetany and neuromuscular irritability. These characteristic metabolic features might be corrected by parathyroid hormone as well as dihydrotachysterol.

In 1942 ALBRIGHT, BURNETT, SMITH and PARSON (1) reported three cases of a syndrome which they called "pseudo-hypoparathyroidism" and which had the same symptomatology, chemical findings and physical

signs as those of hypoparathyroidism, but the cause of the disturbance was due, not to a lack of the parathyroid hormone, but rather to a resistance to it. They also suggested the name of the "Seabright-Bantam Syndrome" as a good example of end-organ unresponsiveness.

The cases, in addition, showed a characteristic facies and body habitus with a round face, a short, stocky stature and short metacarpals except those of index fingers.

Since then about fifteen cases have been described in the literature (2, 3, 7, 9, 10, 12, 14) but none from Scandinavia. A few of the cases reported by LACHMANN in his clinical study from 1941, "Hypoparathyroidism in Denmark," however, show a similar appearance (8).

The hitherto reported cases show a wide variation of the frequency with which individual metacarpal and metatarsal bones are involved and a high frequency of ectopic ossification or calcification. Several of the cases also had a low intelligence quotient. Parathyroid biopsy showed hyperplasia in two cases. The resistance of the action of parathyroid extract in pseudohypoparathyroidism were demonstrated by noting the failure of the serum calcium to rise upon the administration of parathyroid extract and by performing the so called ELLSWORTH-HOWARD test (6). This test is based on the fact that the intravenous administration of 2 ml (200 units) of parathyroid extract to normal individuals and to cases of true hypoparathyroidism is followed by an increase in phosphate excretion in the urine. Cases with pseudohypoparathyroidism, however, with one exception, failed to respond to the parathyroid hormone with a phosphorus diuresis.

Case report

A nine year old school girl was admitted to the Children's Hospital in Sundsvall because of convulsions.

History: Mother and father and her twelve year old sister are intelligent, normal and well-adjusted but mother and sister have partial syndactylism between the second and third toes. An uncle (mother's brother) aged 40 is an imbecile. He is short and stocky because of stunted growth (weight 67.5 kg, height 142 cm) and has stubby hands (no x-ray examination). Serum calcium 12.2 mg/100 ml; serum phosphorus 6.8 mg/100 ml; serum alkaline phosphatase 5.5 units. Family history otherwise negative.

The mother was in good health during the pregnancy and the delivery of the patient was normal. Obesity and short stature had been present since early childhood. She weighed 3.7 kg at birth but her weight increased very soon and during her first year and henceforth it stayed above normal values (Fig. 1). She was breast-fed. She walked at 15 months and talked at 2 years. At seven years she had four convulsive seizures over a period

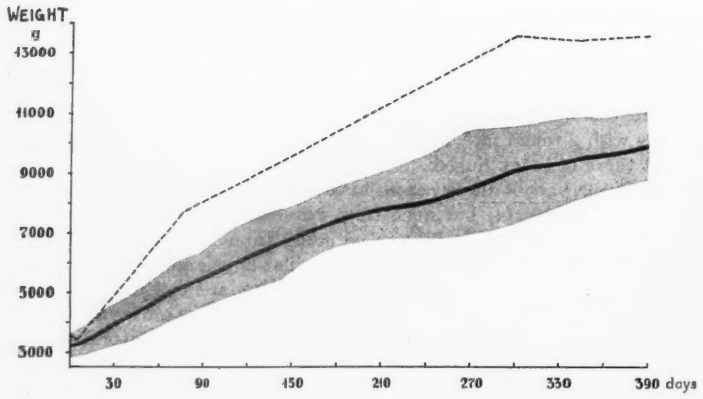

Fig. 1. Weight during first year of life in a case of pseudohypoparathyroidism (– – – –).
Average weight (———) and variations within normal limits (shadowed) in healthy infants. (VON SYDOW, 13.)

of three weeks with loss of consciousness. At the same time she developed whooping cough. At nine years she had another convulsive attack and was now thoroughly examined.

Physical examination: She was of a short thick-set build, had a round face with wide nostrils and stubby hands with the index finger longer than the other fingers (Figs. 2, 3 and 4). Her weight was 38 kg and her height 129 cm. Other measurements: head 54 cm; neck 31 cm; chest 73 cm; abdomen 76 cm. Her skin was dry and her hair coarse and she had a slight conjunctivitis and vulvitis. Chvostek facial reflex and Trousseau sign were positive. There were no cataracts.

Roentgenological examinations: X-rays showed shortness of all metacarpals except those of index fingers in both hands and areas of soft tissue calcification around the left ankle (Fig. 5).

Laboratory data: Serum calcium levels were low, serum phosphorus levels high but alkaline phosphatase concentration normal. The urinary phosphate and calcium excretions were low and the Sulkowitch test of the urine was consistently negative.

ECG revealed consistently a marked increase in the Q-T intervals. The basal metabolic rate was between minus 4 and minus 22. The Terman-Merrill mental test gave an intelligence quotient of 71.

Further details are shown in Table 1.

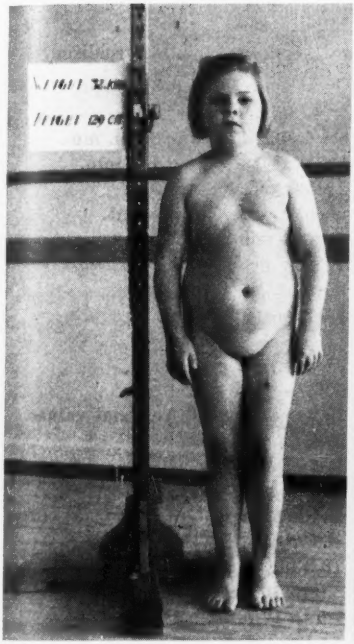

Fig. 2.

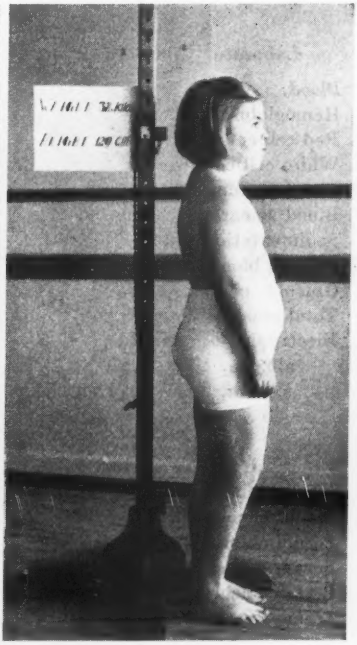

Fig. 3.

Girl, aged 9, with pseudohypoparathyroidism.

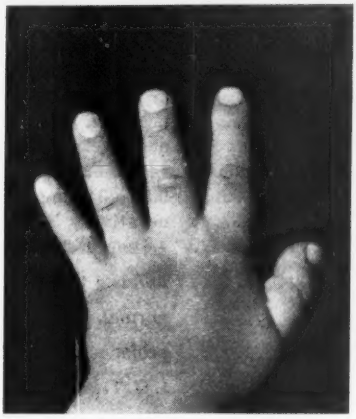

Fig. 4. Stubby hand in a case of pseudohypoparathyroidism.

Table 1.

Laboratory findings in a case of pseudohypoparathyroidism.

Blood:	
Hemoglobin	76 to 96 per cent.
Red cell count	3.8 to 4.6 millions per cu. mm.
White cell count	7 000 to 10 200 per cu. mm.
Platelet count	214 000 per cu. mm.
Blood smears	normal differential count.
Sedimentation rate	2 to 24 mm in 1 hour.
Fasting blood sugar	103 mg per 100 ml.
Glucose tolerance test	normal.
Total plasma protein	7,6 g per 100 ml.
Electrophoretic analysis:	
alb. $+ a_1$	57.8 rel. per cent. }
a_2	5.9 » » »
β	13.2 » » » } normal values.
φ	5.4 » » »
γ	17.7 » » » }
Nonprotein nitrogen	26.5 mg per 100 ml.
Serum cholesterol	133 mg per 100 ml.
Serum chloride	355 mg per 100 ml.
Serum potassium	16.3 mg per 100 ml.
Serum calcium	6.0 to 10.8 mg per 100 ml.
Serum inorganic phosphorus	7.5 to 12.5 mg per 100 ml.
CO_2 capacity	61.1 vol. per cent.
Serum alkaline phosphatase[1]	9.8 to 15.0 units.
Thymol turbidity test	1.4 units.
Takata reaction	negative.
Wassermann reaction	negative.
Urine:	
Albumin test	negative.
Sugar test	negative.
Sediment	negative.
Inorganic phosphorus-excretion	440 to 526 mg in 24 hrs.
Calcium-excretion	9.5 to 34.1 mg in 24 hrs.
Sulkowitch test	negative.
17-ketosteroids	4.4 mg in 24 hrs.
Basal metabolic rate:	minus 4 to minus 22.
Cerebrospinal fluids:	normal.
ECG:	prolonged Q-T intervals.
Mental test (TERMAN-MERRILL):	I. Q. 71.

[1] Method: KING and ARMSTRONG modified by BUCH and BUCH (4).

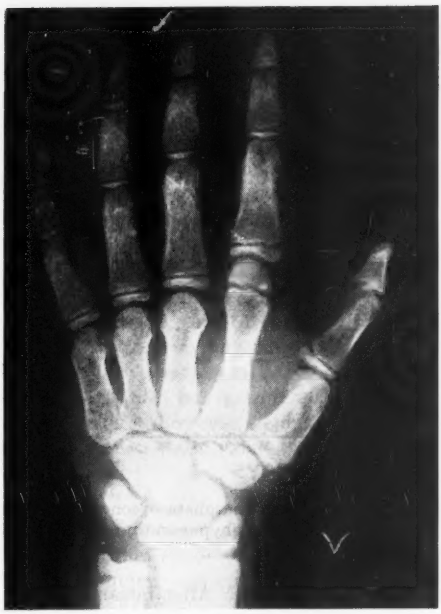

Fig. 5. X-ray of hand showing shortness of all metacarpals except those of index finger.

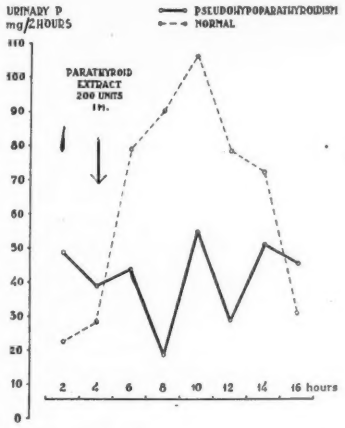

Fig. 6. Modified ELLSWORTH-HOWARD test.

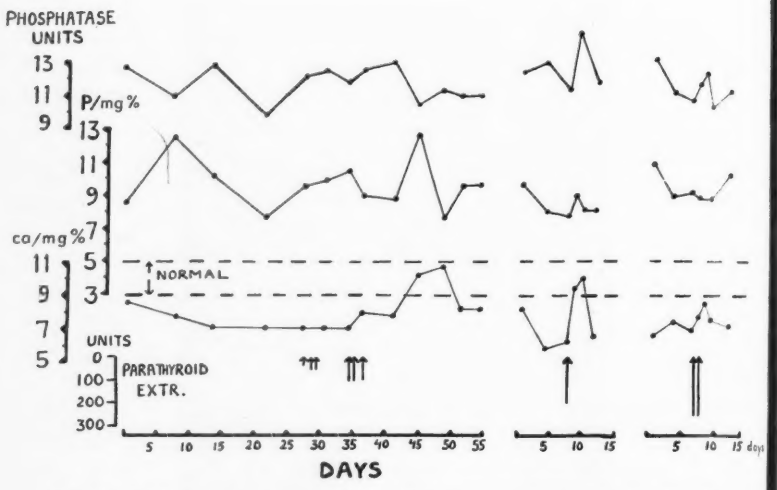

Fig. 7. Calcium, phosphorus and phosphatase concentration in the blood in a case of pseudohypoparathyroidism.

Modified Ellsworth-Howard test. After intramuscular administration of 2 ml (200 units) parathyroid extract ("Paroidin," Parke, Davis & Co.) to the fasting patient there was no increase in phosphate excretion in the urine during the following 40 hours, which contrasted to the pronounced increase in phosphate excretion passed within 12 hours in a normal case of the same age (Fig. 6). The Ellsworth-Howard test had to be modified in this way as this parathyroid extract was not for intravenous administration.

Administration of parathyroid extract. Parathyroid extract ("Paroidin," Parke, Davis & Co.) was given four times (Fig. 7). The first time 100 units were given over three days. The second time 300 units were given over four days and one week later the serum calcium levels temporarily rose to normal values. The third time 200 units were given in one dose (for the Ellsworth-Howard test) and the following day serum calcium was increased from 6.4 to 9.4 and the day after to 10.0 mg per cent. The fourth time 500 units were given for two days and were followed by a insignificant increase of the serum calcium. Thus the changes in the serum calcium levels following administrations of parathyroid extract in these doses were small and insignificant. The whole time the serum phosphorus levels were high and the alkaline phosphatase concentration normal.

Administration of dihydrotachysterol. "A. T. 10" (Bayer), 1 ml (5 mg dihydrotachysterol) daily, was given for one month with no effect on the serum phosphorus levels, while the serum calcium was kept on a level of the lowest limit for the normal values.

Summary

Since ALBRIGHT et al. (1942) reported the first three cases of a syndrome, which they called pseudo-hypoparathyroidism, about fifteen cases have been described. Another case of pseudo-hypoparathyroidism is described. The patient was a girl, aged 9, with short, thick-set figure, round face, stubby hands with shortness of all metacarpals except those of index fingers, soft tissue calcifications, low IQ, hyperphosphatemia and hypocalcemia. She has an imbecile uncle with the same habitus. After administration of parathyroid extract there was no phosphate diuresis response and a small but insignificant increase of serum calcium levels. Dihydrotachysterol, however, kept the serum calcium on a level of the lowest limit of the normal values.

Pseudohypoparathyroïdisme.

Depuis que ALBRIGHT et ses collaborateurs ont rapporté, en 1942, les premiers trois cas d'un syndrome, qu'ils appellent pseudohypoparathyroïdisme, environ quinze cas ont été décrits. L'auteur rapporte un nouveau cas de pseudohypoparathyroïdisme chez une fillette agée de 9 ans, petite d'aspect et épaisse, elle présente un visage arrondi, des mains carrées avec raccourcissement de tous les métacarpiens, excepté ceux des index, des calcifications au niveau des tissus mous, un quotient intellectuel bas, hyperphosphatémie et hypocalcémie. Elle a un oncle imbécile avec le même habitus. L'administration d'extrait parathyroïdien n'entraîna pas de diurèse phosphatée, et une légère mais insignifiante augmentation du taux de calcium sérique. Le dihydrotachystérol cependant, maintint le calcium sérique au niveau de la limite inférieure de la valeur normale.

Pseudohypoparathyreoidismus.

Seit ALBRIGHT u. Mitarbeiter 1942 über die ersten 3 Fälle eines Syndroms berichteten, welches sie Pseudohypoparathyreoidismus nannten, sind inzwischen ca. 15 Fälle beschrieben worden. Der Autor berichtet über einen neuen Fall von Pseudohypoparathyreoidismus, ein 9-jähriges Mädchen, mit dicker Statur, rundem Gesicht, plumpen Händen, Verkürzung aller Metacarpalen mit Ausnahme der des Zeigefingers, Weichteilverkalkungen, niedrigem IQ, Hyperphosphatämie und Hypocalcämie. Sie hat einen imbezilen Onkel mit dem gleichen Habitus. Nach Zufuhr von Parathyreoideaextrakt kam keine Phosphatdiurese zustande und nur

eine unbedeutende Zunahme des Serumkalziumspiegels. Dihydrotachysterol konnte den Serumkalziumspiegel immerhin auf der niedrigsten Grenze der Normalwerte halten.

Pseudohipoparatiroidismo.

Desde que ALBRIGHT y colaboradores en 1942 comunicaron por primera vez 3 casos de un síndrome por ellos llamado pseudohipoparatiroidismo se han descrito unos 15 casos. El autor presenta uno de ellos en una niña de 9 años de talla corta, figura gruesa, cara redondeada y manos recias con metacarpianos cortos, excepto los correspondientes al dedo índice. Calcificaciones en los tejidos blandos, C. I. bajo, hipofosfatemia e hipocalcemia. Esta niña tenía un tio con una idiocia que presentaba el mismo aspecto. Tras la administración de extracto paratiroideo no se produjo una respuesta de diuresis fosfática y solo una pequeña e insignificante aumento del calcio sérico. La administración de dihidrotaquiesterol produjo sin embargo un aumento de la calcemia hasta el límite inferior de los valores normales.

References

1. ALBRIGHT, F., BURNETT, C. H., SMITH, P. H. and PARSON, W.: Pseudohyoparathyroidism, An example of "Seabright Bantam Syndrome"; Report of Three Cases. Endocrinology *30:* 922, 1942.
2. ALBRIGHT, F. and REIFENSTEIN, E. C., Jr.: The Parathyroid Glands and Metabolic Bone Disease: Selected Studies, The Williams and Wilkins Company, Baltimore, 1948.
3. BAKWIN, H., GORMAN, W. F. and ZIEGRA, S. R.: Pseudohypoparathyroid tetany. J. Pediat. *36:* 567, 1950.
4. BUCH, I. and BUCH, H.: An improved King and Armstrong method for the determination of phosphatase activity in blood serum. Acta med. Scandinav. *101:* 211, 1939.
5. COLLIP, J. B.: The extraction of the parathyroid hormone, which will prevent or control parathyroid tetany and which regulates the level of blood calcium. J. Biol. Chem. *63:* 395, 1925.
6. ELLSWORTH, R. and HOWARD, J. E.: Studies on the physiology of the parathyroid glands; VII. Some responses of normal human kidneys and blood to intravenous parathyroid extract. Bull. Johns Hopkins Hosp. *55:* 296, 1934.
7. ELRICK, H., ALBRIGHT, F., BARTTER, F. C., FORBES, A. P. and REEVES, J. D.: Further studies on pseudo-hypoparathyroidism: report of four new cases. Acta Endocrinol. *5:* 199, 1950.
8. LACHMANN, A.: Hypoparathyroidism in Denmark. A clinical study. Acta med. Scandinav. Suppl. 121: 1, 1941.
9. LOWE, C. U., ELLINGER, A. J., WRIGHT, W. S. and STAUFFER, H. M.: Pseudohypoparathyroidism (The Seabright Bantam Syndrome). J. Pediat. *36:* 1, 1950.
10. PETERMAN, M. G. and GARVEY, J. L.: Pseudohypoparathyroidism. Case report. Pediatrics *4:* 790, 1949.
11. SANDSTRÖM, I.: Om en ny körtel hos menniskan och åtskilliga däggdjur. Uppsala läkarefören. förhandl. *15:* 441, 1880.
12. SELYE, H.: Textbook of Endocrinology. Acta Endocrinol. Inc., Montreal, Canada, 1949.

13. von Sydow, G.: The weight of healthy breast fed infants during the first year of life. Acta Paediat. *28:* 8, 1940.
14. Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. Charles G. Thomas, Springfield, Ill., U.S.A., 1950.

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SUMMARY OF SUPPLEMENT

Ragnar Berfenstam: *Studies on Blood Zinc.* A clinical and experimental investigation into the zinc content of plasma and blood corpuscles with special reference to infancy. (Acta Pædiat. 41. Suppl. 87, 1952.)

1. The author has introduced a modification in *the methods* usually adopted in the past for zinc analysis. Instead of ashing the material the zinc is extracted with strong hydrochloric acid and the protein precipitated with trichloroacetic acid. Zinc determination is performed on the clear supernatant fluid using a dithizone method.

2. The *stability of the zinc protein combination* at different degrees of acidity has been studied in dialysis tests. The zinc in both plasma and haemolysed corpuscles separated in increasing amount from the protein complex when the pH value fell below the neutral point.

3. The *capacity* of the plasma and haemolysed blood corpuscles *to bind additional zinc* was studied in dialysis tests. It proved to be very high indeed admitting non-dialysable combination even in concentrations of zinc very many times higher than normal. Thus, contrary to iron, the plasma does not show a saturation limit for zinc within the range of this investigation.

4. The *plasma zinc* in 126 healthy adults shows an average level of 109 ± 2 µg %.

The plasma zinc level in 10 foetuses between the 4th and 6th months is 300 ± 31 µg %, in 16 premature infants 187 ± 20 µg %, in 39 full-term newborn infants 125 ± 5 µg %. Later in infancy the plasma zinc level is somewhat higher than the adult value. Thus the plasma zinc shows a continuous fall from the very high values during the foetal stage.

During pregnancy the plasma zinc shows a definite fall with values 20—25 % below normal at the end of gestation.

5. The *zinc content of the blood corpuscles* in 84 healthy adults was 1244 ± 20 µg %.

During the foetal stage the zinc content of the blood corpuscles is very low and rises only slowly, with a mean value at term of 376 ± 19 µg %. After birth the values initially rise more rapidly, values of 800 µg % being reached by the end of the first year, and adult level by adolescence.

6. A comparison between *mother and child at birth* shows higher plasma values but much lower blood corpuscle values in the child as compared with the mother.

The possible transfer of zinc from mother to foetus by means of the plasma zinc is discussed.

7. There is a correlation between the behaviour of blood *corpuscle zinc* and that of *carbonic anhydrase*, both showing a similar successive increase with age.

8. The infant receives considerable quantities of *zinc from the food*. Analyses of breast milk revealed that the zinc concentration varied. In colostrum it is as high as 2000 µg %, after a month or two 300—500 µg %, and later on it falls still lower.

Balance tests performed on a limited number of children indicated that the organism does not retain more than small quantities of the zinc supplied with the food.

9. *In experiments on rabbits* the following observations were made.

a) Intravenous zinc dosage in the form of zinc salt solution gives a considerable increase in the zinc of the circulating blood. Rabbits of normal size tolerate a dose of 20—30 mg zinc, which quantity gives plasma zinc values of over 10 000 µg %.

b) Oral administration of zinc salt gives a definite but transient

rise in the plasma zinc. After prolonged oral administration of zinc a single dose of zinc produces higher plasma values that persist for a considerable time. 0.25 g zinc daily is tolerated by adult animals for a long period without any toxic signs.

c) Intravenous as well as oral zinc administration gives a rise not only in the plasma zinc level but also in the content of zinc in the blood corpuscles. The high corpuscle zinc persists only as long as the plasma zinc values are definitely raised. The increase of the zinc content of the blood corpuscles thus provoked is not reflected in an increased carbonic anhydrase activity.

d) In experiments with pregnant rabbits it was demonstrated that an increased plasma zinc level in the dam gives rise to an increased plasma zinc level in the offspring. This increased level in the plasma does not lead to *persistently* high levels in the corpuscle zinc of the newborn animals.

e) The progressive increase in corpuscle zinc of the young animals during the first month of life does not seem to be affected by artificially increased zinc intake with the food.

NEWS AND COMMENTS

Die 52. Tagung der *Deutschen Gesellschaft für Kinderheilkunde* findet vom 1. bis 4. September d. Js. *in Bayreuth*, unter dem Vorsitz von Professor ADAM, Erlangen statt. Als Hauptvorträge sind vorgesehen: I. „Acute Ernährungsstörungen des Säuglings", Referenten: G. ILGNER, Erlangen, O. H. BRAUN, Heidelberg, HUNGERLAND, Giessen, H. KLEINSCHMIDT, Göttingen. II. „Ernährung und Aufzucht von Frühgeborenen", Referenten: E. ROMINGER, Kiel, H. WILLI, Zürich. III. „Scenotest", v. STAABS, Berlin. IV. „Pharmakologie des D-Vitamins", W. GRAB, Wuppertal-Elberfeld. Vortragsmeldungen (Auswahl begrenzt) mit genauer Inhaltsangabe werden bis zum 15. Juni 1952 an den Vorsitzenden (Erlangen, Universitäts-Kinderklinik) erbeten. Es ist vorgesehen, die Tagung mit einer *Wissenschaftlichen Ausstellung* zu verbinden.

BOOK REVIEW

J. W. C. De Groot: *Angiocardiography as a Diagnostic Aid in Congenital Heart Disease.* Keesing, Amsterdam, 1951. Price Fl. 7.50.

A short review of results obtained by other investigators is given in the first part of the book. It would have been of value to give a more detailed discussion on contrast media and anesthetics. According to our experience avertin per rectum is safe and has the advantage of a smooth induction. This would have been worth mentioning. The section on normal angiocardiograms is much too short. Thorough knowledge of the *normal* angiocardiogram is necessary when interpreting pathologic angiocardiograms; pictures and schematic drawings of the former are lacking. The clinical material of 51 cases is presented in the second part of the book. The author has used equipment permitting 9—20 cassettes to be exposed at a rate of 2—4 per second. This technique may explain some statements which would not otherwise have been made if a faster rate of exposures had been used. The interpretation of the angiocardiograms demonstrates experience and good criticism and the role of angiocardiography in the clinical analysis of congenital heart disease is well exemplified. Unfortunately the illustrations are not good, too few and not well reproduced. In at least three of them details explained in the legends do not show up. This monograph is presented as an attempt to pool the results of numerous single studies on the subject of angiocardiography. The book can, however, be considered as a short and easy introduction to clinical angiocardiography.

John Lind, Stockholm.